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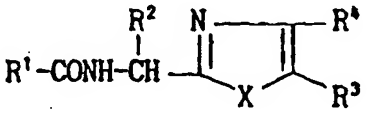
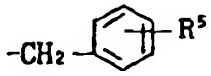
(54) Title: NEW INDOLYL AND BENZOFURANYL CARBOXAMIDES AS INHIBITORS OF NITRIC OXIDE PRODUCTION

(57) Abstract

A compound of formula (I) wherein R^1 is indolyl or benzofuranyl; R^2 is hydrogen, lower alkylthio(lower)alkyl or a group of formula (1) in which R^5 is hydrogen, lower alkoxy or halogen; R^3 is hydrogen, quinolyl or phenyl which may have a suitable substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkylthio and halogen; R^4 is hydrogen or optionally esterified carboxy; and X is S or NR^6 in which R^6 is hydrogen, lower alkyl or a group of formula (2) in which R^7 is lower alkyl or lower alkoxy, and a pharmaceutically acceptable salt thereof, which possess a strong inhibitory activity on the production of nitric oxide (NO), and are useful for prevention and/or treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, and the like.



(I)



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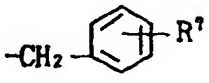

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DESCRIPTION

NEW INDOLYL AND BENZOFURANYL CARBOXAMIDES AS INHIBITORS OF NITRIC OXIDE PRODUCTION

TECHNICAL FIELD

This invention relates to new amide compounds and pharmaceutically acceptable salts thereof which are useful as medicament.

BACKGROUND ART

Some peptide compounds have been known as described, for example, in EP 0 394 989 A2.

DISCLOSURE OF INVENTION

This invention relates to new amide compounds.

One object of this invention is to provide the new and useful amide compounds and pharmaceutically acceptable salts thereof which possess a strong inhibitory activity on the production of nitric oxide (NO).

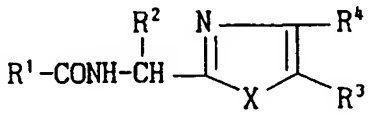
Another object of this invention is to provide a process for the preparation of the amide compounds and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said amide compound or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a use of said amide compounds or pharmaceutically acceptable salts thereof as a medicament for prophylactic and therapeutic treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, synovitis, shock (e.g., septic shock, etc.), diabetes (e.g., insulin-dependent diabetes mellitus, etc.), diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, glomerulonephritis, peptic ulcer, inflammatory bowel disease (e.g., ulcerative colitis, chronic colitis, etc.), cerebral

infarction, cerebral ischemia, cerebral hemorrhage, migraine, rheumatoid arthritis, gout, neuritis, postherpetic neuralgia, osteoarthritis, osteoporosis, systemic lupus erythematosis, rejection by organ transplantation, asthma, metastasis, Alzheimer's disease, arthritis, CNS disorders, and the like in human being and animals.

The object amide compounds of the present invention are novel and can be represented by the following general formula (I) :

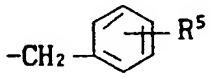


(I)

wherein

R^1 is indolyl or benzofuranyl;

R^2 is hydrogen, lower alkylthio(lower)alkyl or a group of the formula:



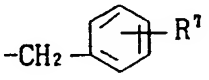
in which R^5 is hydrogen, lower alkoxy or halogen;

R^3 is hydrogen, quinolyl or phenyl which may have a suitable substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkylthio and halogen;

R^4 is hydrogen or optionally esterified carboxy; and

X is S or NR^6

in which R^6 is hydrogen, lower alkyl or a group of the formula:



in which R^7 is lower alkyl or lower alkoxy.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and include, for example, a salt with a base or an acid addition salt such as a salt with an inorganic

base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, citrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); and a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, gultamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "lower alkylthio" and "lower alkylthio(lower)alkyl" include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl, and in which more preferred one is C_1-C_4 alkyl.

Suitable "lower alkoxy" includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy and hexyloxy, and in which more preferred one is C_1-C_4 alkoxy.

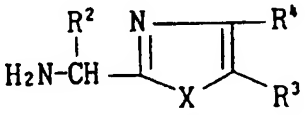
Suitable "halogen" includes, for example, fluorine, bromine, chlorine and iodine.

"Optionally esterified carboxy" includes carboxy and esterified carboxy. Suitable examples of said ester include lower alkyl ester

(e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, tert-pentyl ester, hexyl ester, etc.); lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.); lower alkoxy(lower)alkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxymethyl ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.); mono(or di or tri)-aryl(lower)alkyl ester, for example, mono(or di or tri)phenyl(lower)-alkyl ester which may have one or more suitable substituent(s) [e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.]; and aryl ester which may have one or more suitable substituent(s) such as substituted or unsubstituted phenyl ester (e.g., phenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, 4-chlorophenyl ester, 4-methoxyphenyl ester, etc.).

The object compound (I) of the present invention can be prepared by the following process.

Process (1)



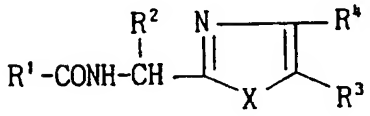
(II)

or its reactive derivative at the amino group, or a salt thereof

R^1-COOH

(III)

or its reactive derivative at the carboxy group, or a salt thereof



(I)

or a salt thereof

wherein R^1, R^2, R^3, R^4 and X are each as defined above.

The starting compounds can be prepared by the method of Preparation mentioned below or by a process known in the art for preparing structually analogous compounds thereto.

The process for preparing the object compound is explained in detail in the following.

Process (1)

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group, or a salt thereof with the compound (III) or its reactive derivative at the carboxy group, or a salt thereof.

Suitable reactive derivative of the compound (II) includes Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (II) with phosphorus trichloride or phosgene.

Suitable reactive derivative of the compound (III) includes an acid halide, an acid anhydride and an activated ester. The suitable example may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid

(e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); or an ester with an N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.). These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

When the compound (III) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide; N,N-carbonyl-bis-(2-methylimidazole); pentamethylene-ketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride;

triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Suitable salts of the starting compounds and their reactive derivatives in Process (1) can be referred to the ones as exemplified for the compound (I).

The compounds obtained by the above process can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all of such isomers and mixtures thereof are included within the scope of this invention.

The object compounds (I) and pharmaceutically acceptable salts thereof include solvates [e.g., enclosure compounds (e.g., hydrate, etc.)].

The object compounds (I) and pharmaceutically acceptable salts thereof possess a strong inhibitory activity on the production of nitric oxide (NO).

Accordingly, the object compounds (I) and pharmaceutically

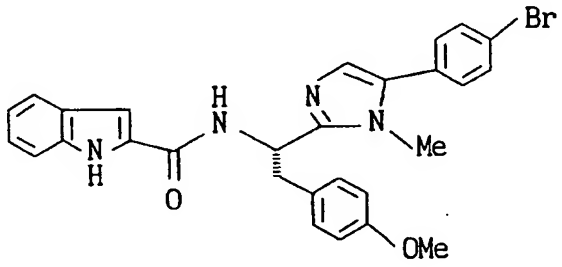
acceptable salts thereof are expected to possess a nitric oxide synthase (NOS)-inhibitory activity or a NOS-production inhibitory activity.

Accordingly, they are useful for prevention and/or treatment of NO-mediated diseases such as adult respiratory distress syndrome, cardiovascular ischemia, myocarditis, heart failure, synovitis, shock (e.g., septic shock, etc.), diabetes (e.g., insulin-dependent diabetes mellitus, etc.), diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, glomerulonephritis, peptic ulcer, inflammatory bowel disease (e.g., ulcerative colitis, chronic colitis, etc.), cerebral infarction, cerebral ischemia, cerebral hemorrhage, migraine, rheumatoid arthritis, gout, neuritis, postherpetic neuralgia, osteoarthritis, osteoporosis, systemic lupus erythematosis, rejection by organ transplantation, asthma, metastasis, Alzheimer's disease, arthritis, CNS disorders, and the like in human being and animals.

In order to illustrate the usefulness of the object compound (I), the pharmacological test result of the representative compound of the compound (I) is shown in the following.

Test Compound :

(a)



Test : Assay for inhibitory activity on the production of nitric oxide

The murine macrophage cell line RAW264.7 (American Type Culture Collection, No. TIB71) was used in this study. RAW264.7 cells were grown on F75 plastic culture flasks at 37℃, 5% in Dulbecco's

modified Eagle's medium (DMEM) supplemented with L-glutamine, penicillin, streptomycin and 10% heat-inactivated fetal bovine serum. They were removed from culture flasks by rubber cell scraper and were centrifuged and resuspended in DMEM without phenol red. They were plated in 96-well microtiter plates (10^5 cells per well) and allowed to adhere over 2 hours. The test samples were added and the cells were preincubated for 1 hour. Thereafter the cells were activated with both of lipopolysaccharide (LPS) (1 μg/ml) and interferon γ (INF γ) (3 u/ml) for 18-24 hours. An equal volume of Griess reagent (1% sulfanilamide/0.1% N-naphthylethylenediamine dihydrochloride/2.5% H_3PO_4) was added and the cells were incubated at room temperature for 10 minutes. The absorbance was read at 570 nm using microplate reader and NO_2^- was measured using $NaNO_2$ as a standard.

Test result :

Test compound (10^{-5}M)	Inhibition (%)
(a)	100

For therapeutic administration, the object compound (I) of the present invention and pharmaceutically acceptable salts thereof are used in the form of a conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee or suppository, or in a liquid form such as solution, suspension or emulsion for injection, intravenous drip, ingestion, eye drop, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered in a unit dose of 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, body weight and conditions of the patient or administering method.

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

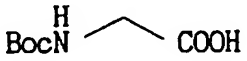
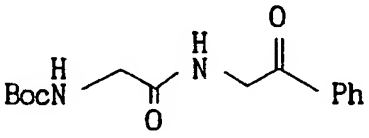
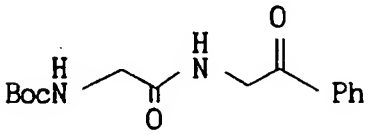
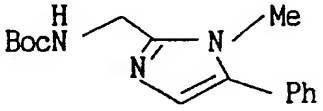
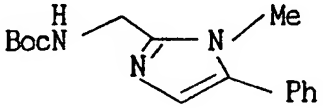
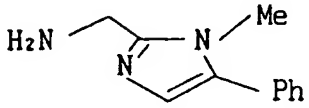
In the following Examples and Preparations, there are employed the other abbreviations in addition to the abbreviations adopted by the IUPAC-IUB (Commission on Biological Nomenclature).

The abbreviations used are as follows.

Boc : t-butoxycarbonyl
Et : ethyl
Me : methyl
Ph : phenyl
Ts : p-toluenesulfonyl

The starting compounds used and the object compounds obtained in the following Preparations and Examples are given in the Tables as below, in which the formulae of the starting compounds are in the upper and the formulae of the object compounds are in the lower, respectively.

Table

Preparation No.	Formula
1	
	
2	
	
3	
	

Table

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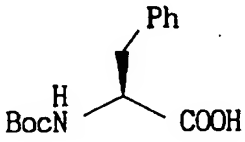
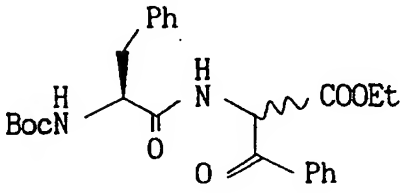
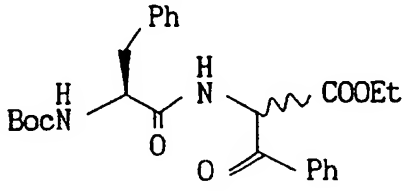
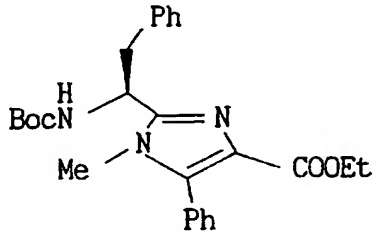
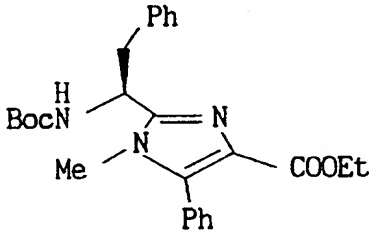
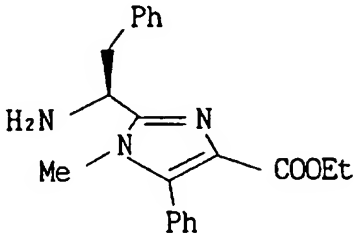
4	
	
5	
	
6	
	

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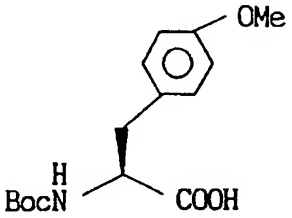
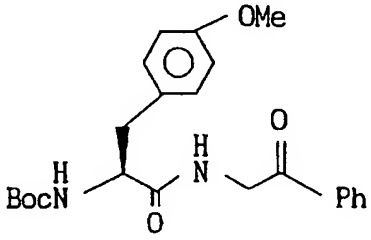
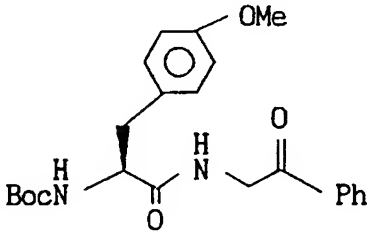
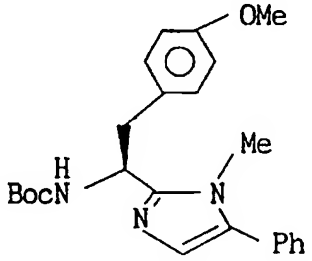
7	
	
8	
	

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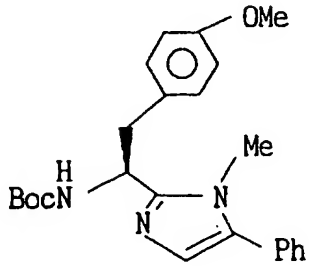
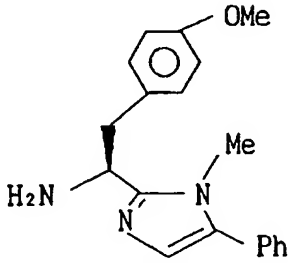
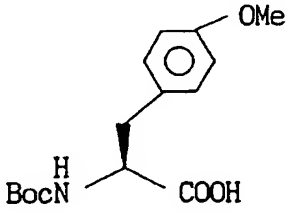
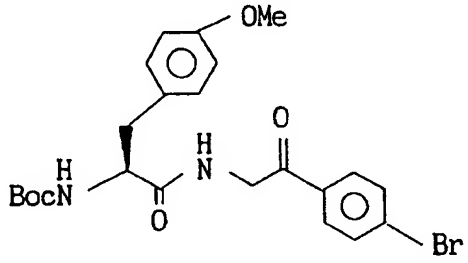
9	
	
10	
	

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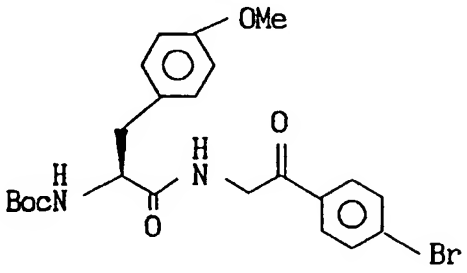
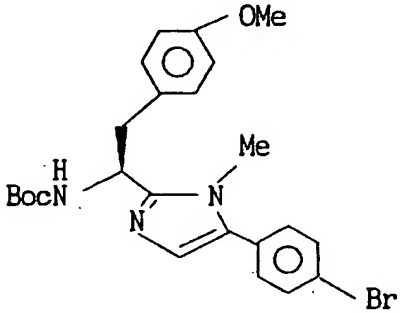
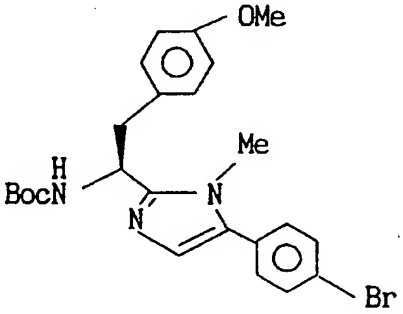
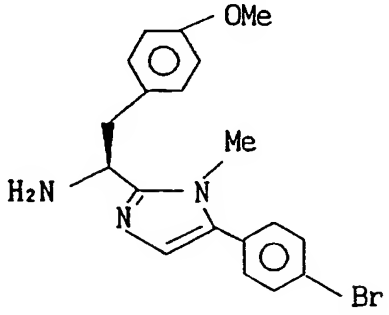
11	
	
12	
	

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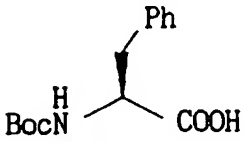
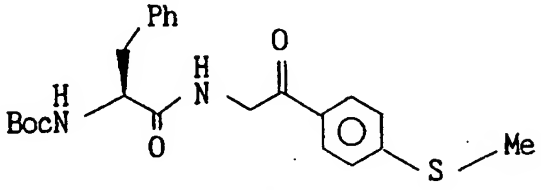
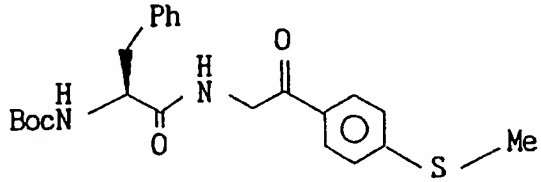
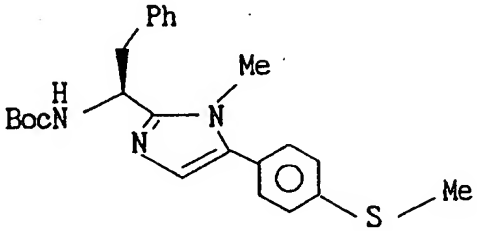
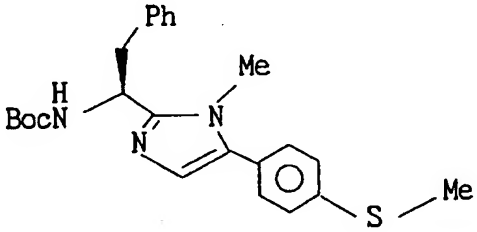
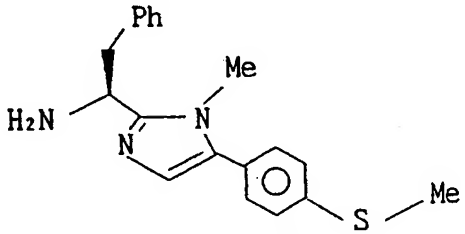
13	
	
14	
	
15	
	

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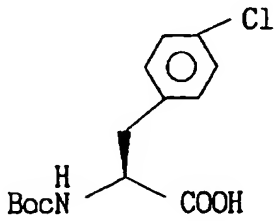
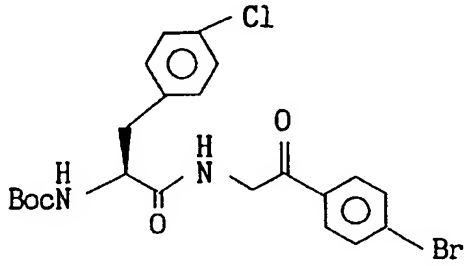
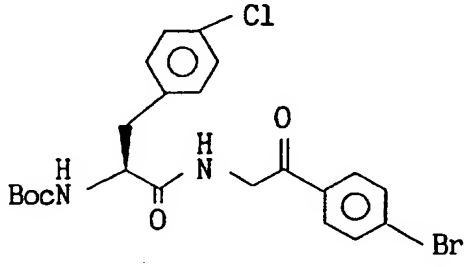
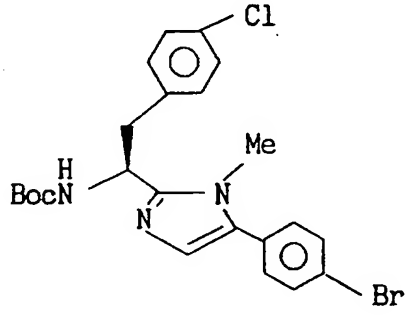
16	
	
17	
	

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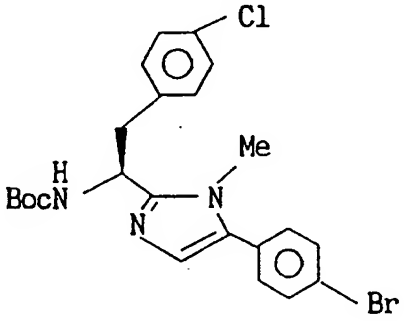
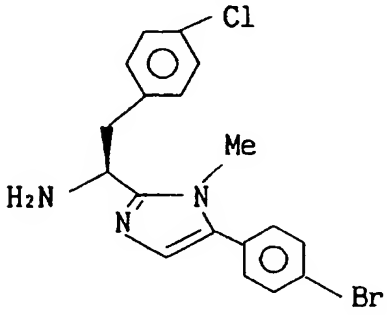
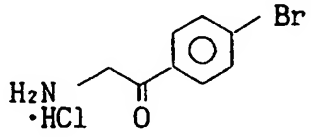
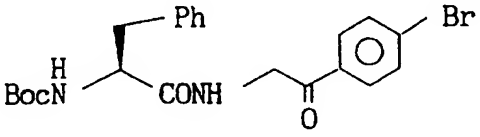
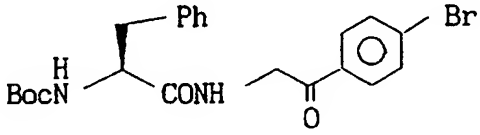
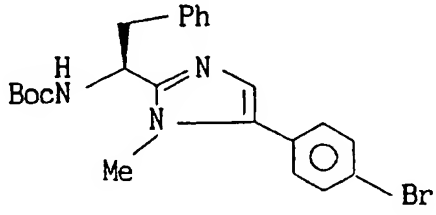
18	
	
19	
	
20	
	

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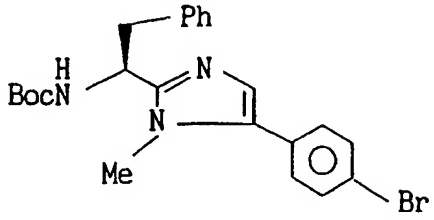
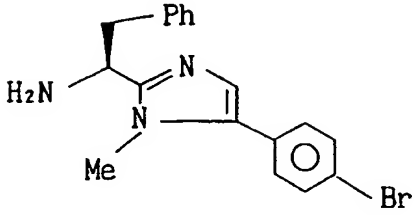
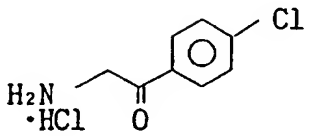
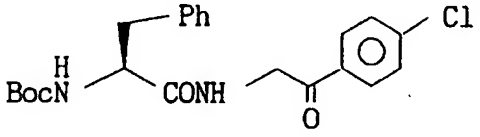
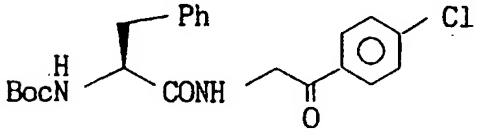
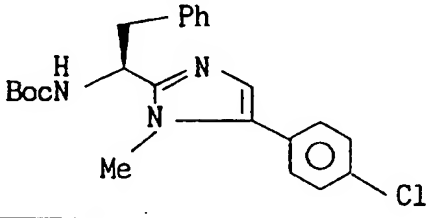
21	
	
22	
	
23	
	

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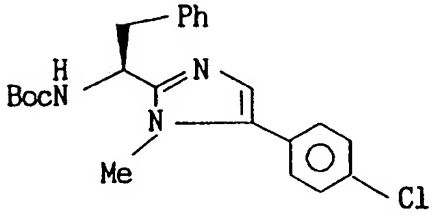
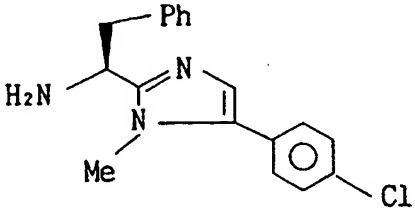
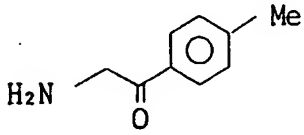
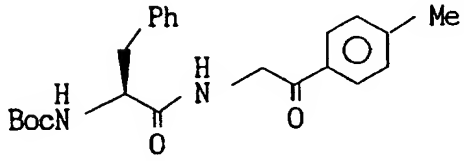
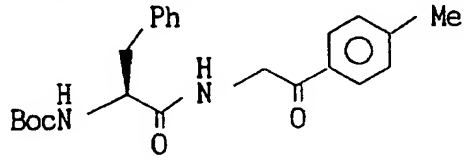
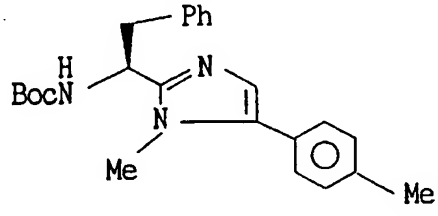
24	
	
25	
	
26	
	

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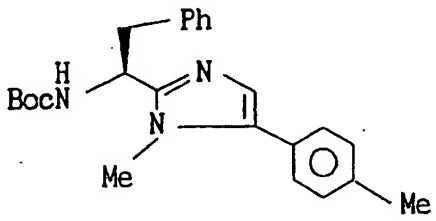
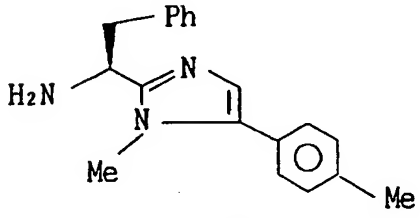
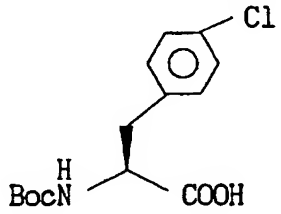
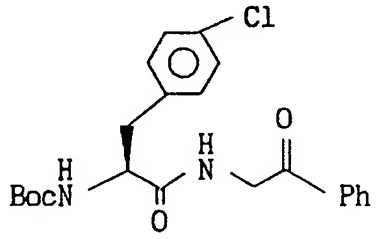
27	
	
28	
	

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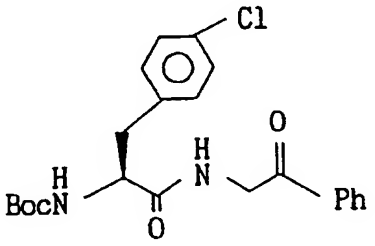
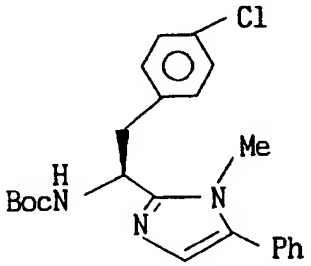
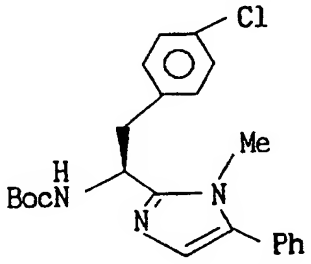
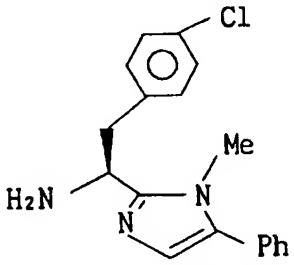
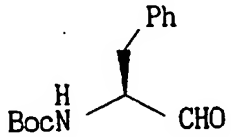
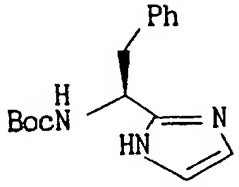
29	
	
30	
	
31	
	

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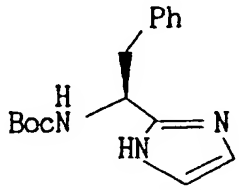
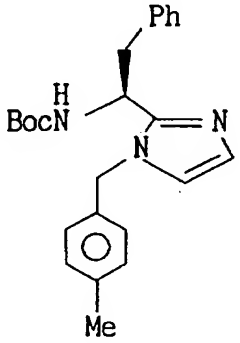
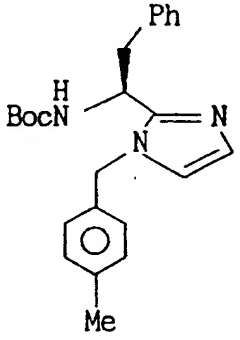
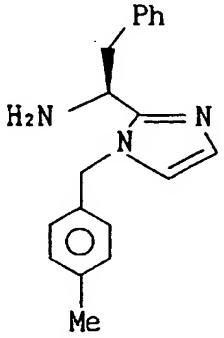
32	
	
33	
	

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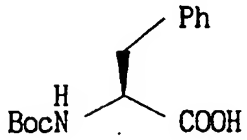
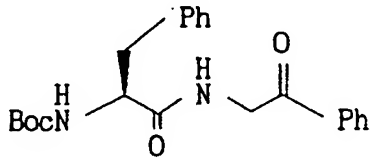
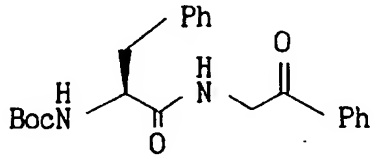
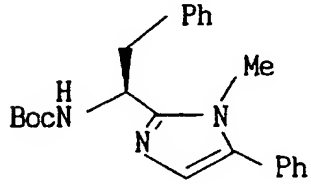
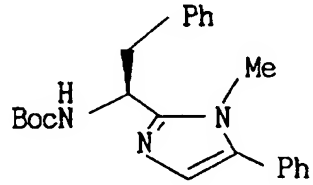
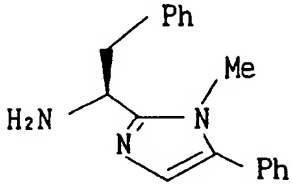
34	
	
35	
	
36	
	

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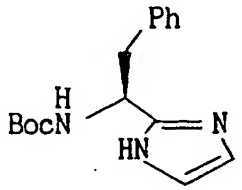
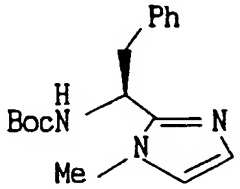
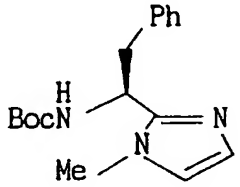
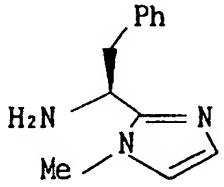
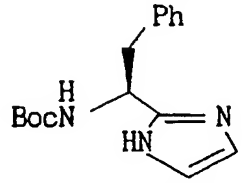
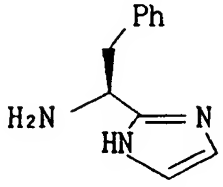
37	
	
38	
	
39	
	

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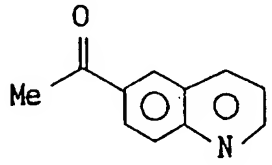
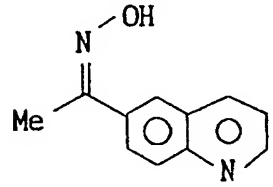
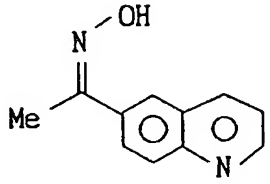
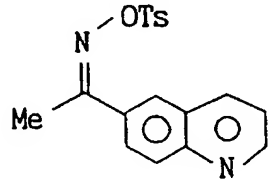
40	
	
41	
	

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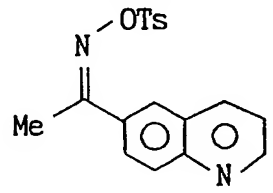
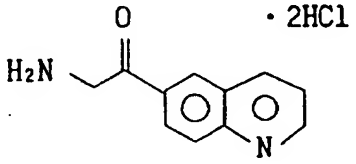
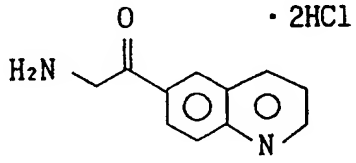
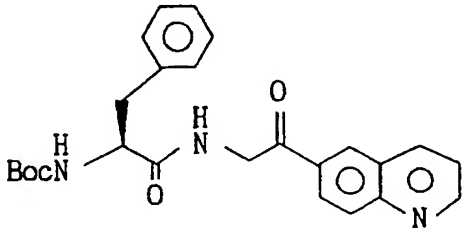
42	
	
43	
	

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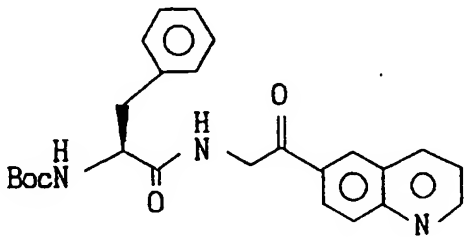
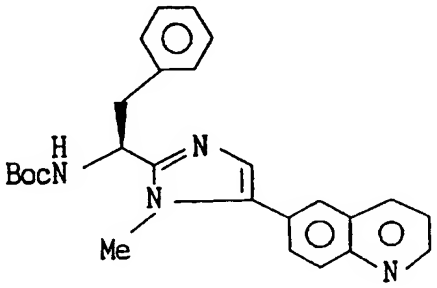
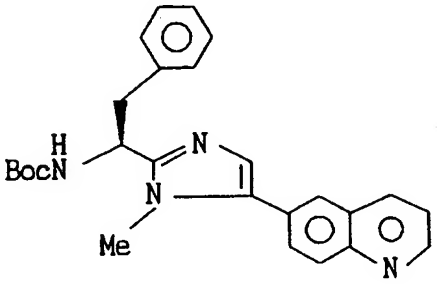
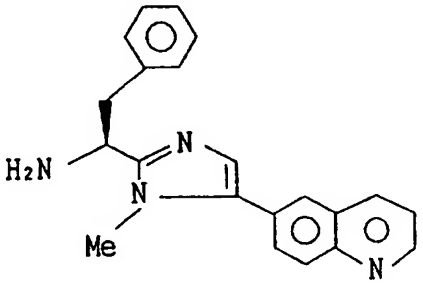
44	
	
45	
	

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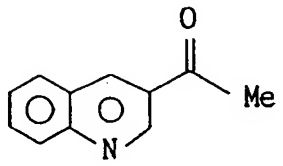
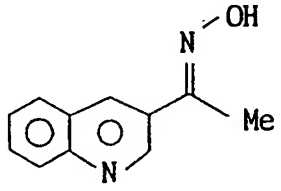
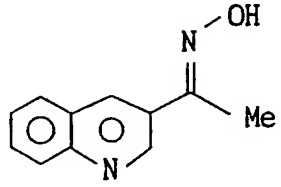
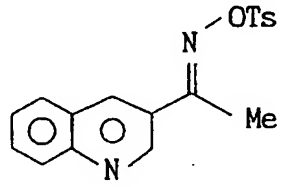
46	
	
47	
	

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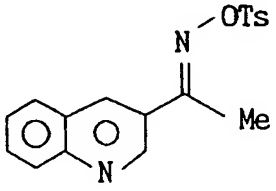
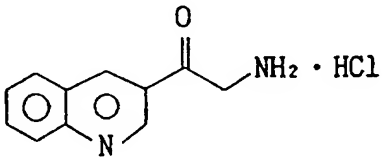
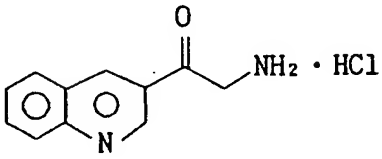
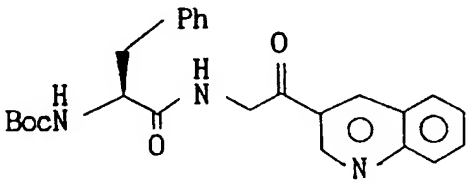
48	
	
49	
	

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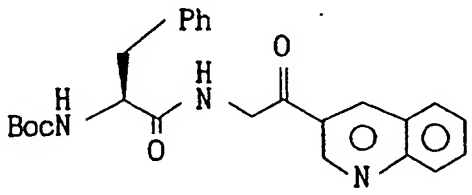
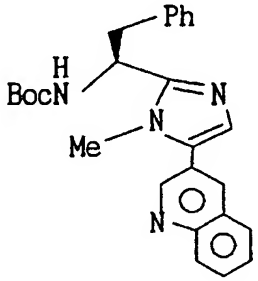
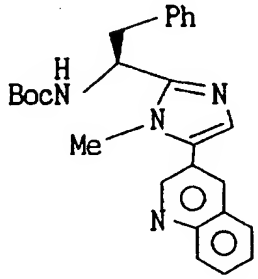
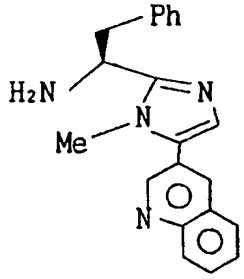
50	
	
51	
	

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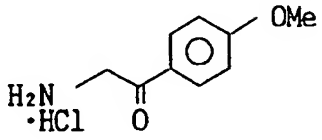
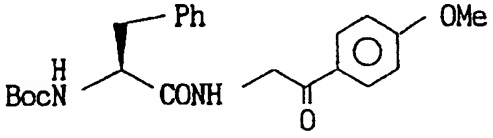
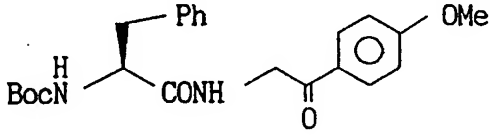
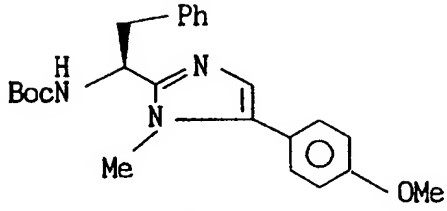
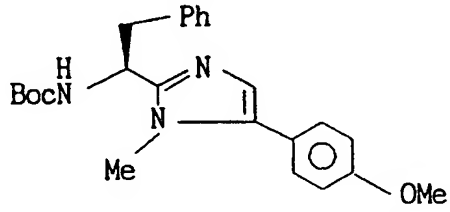
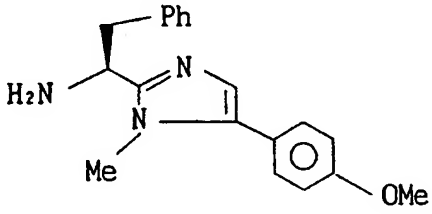
52	
	
53	
	
54	
	

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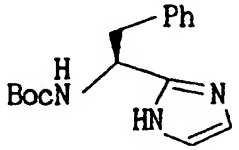
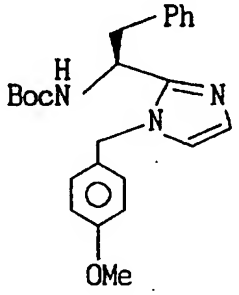
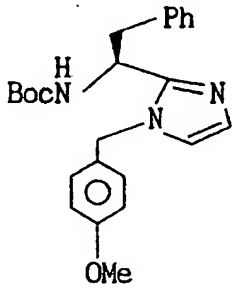
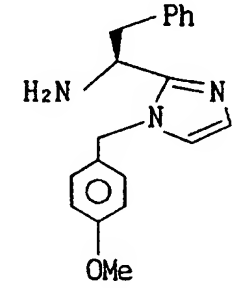
55	
	
56	
	

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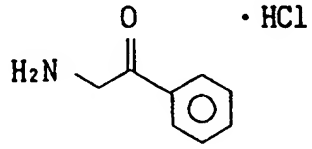
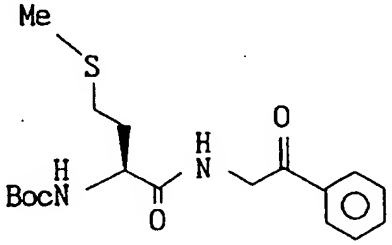
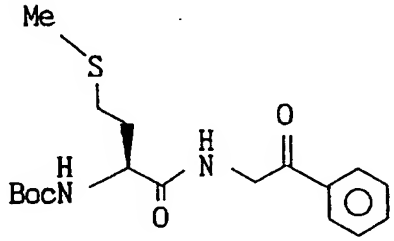
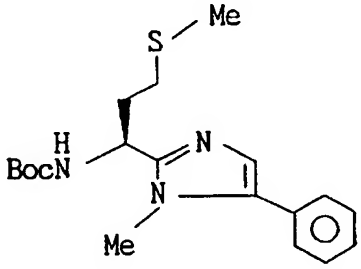
57	
	
58	
	

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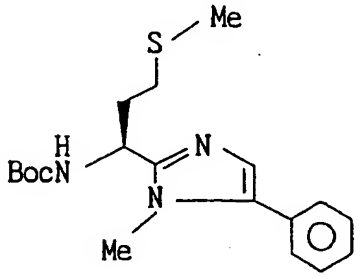
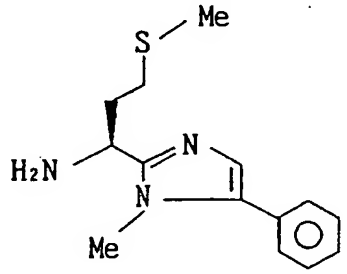
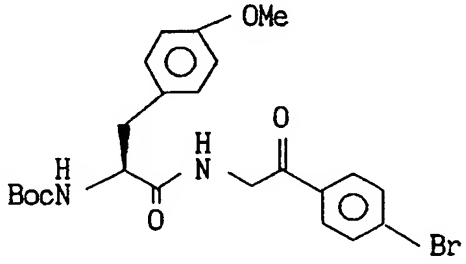
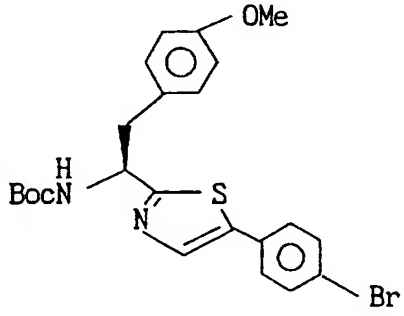
59	
	
60	
	

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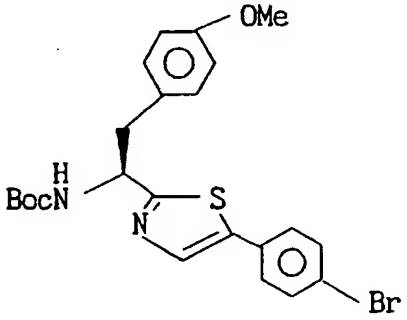
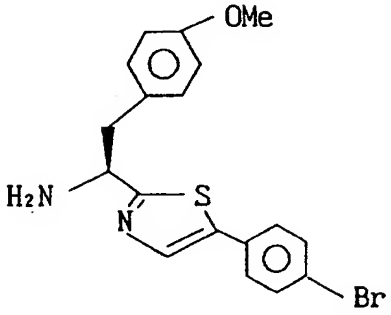
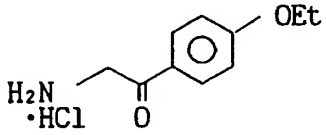
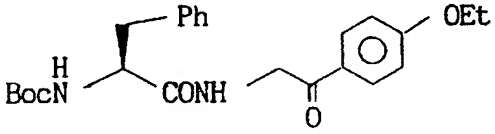
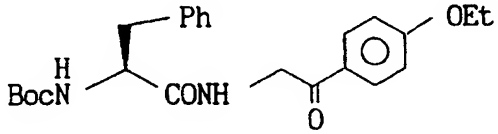
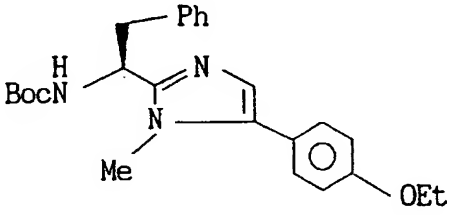
61	
	
62	
	
63	
	

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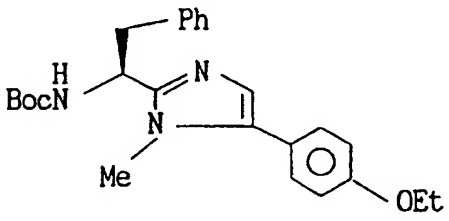
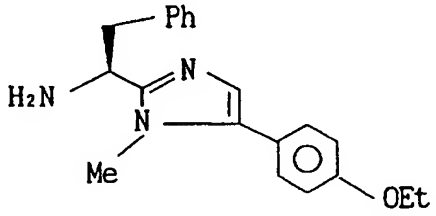
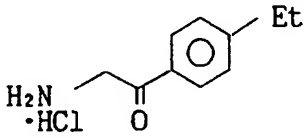
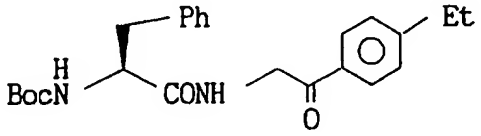
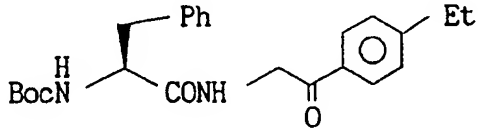
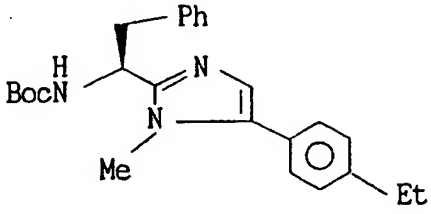
64	
	
65	
	
66	
	

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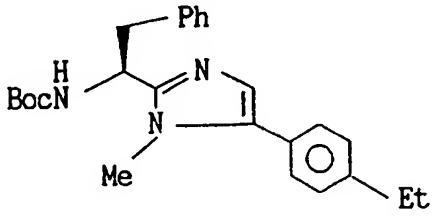
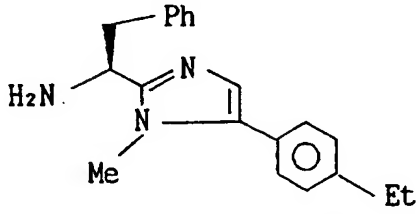
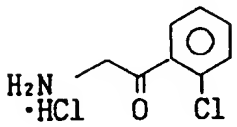
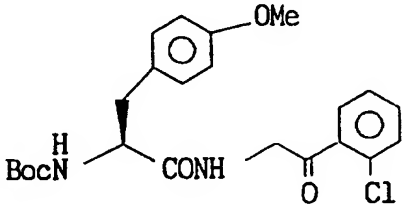
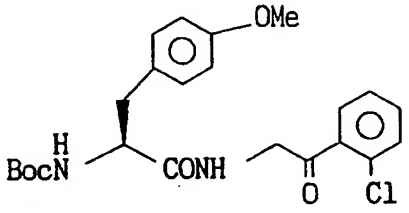
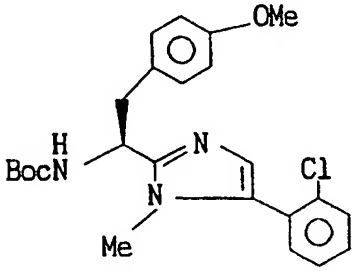
67	
	
68	
	
69	
	

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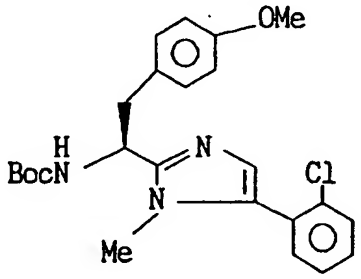
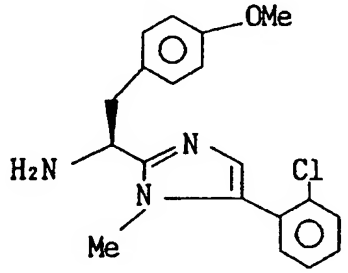
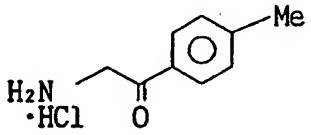
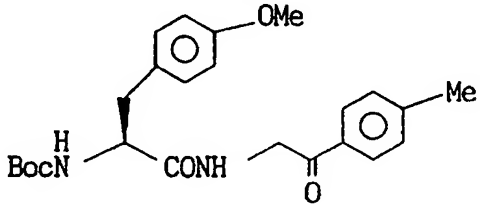
70	
	
71	
	

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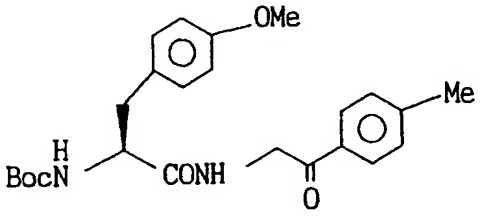
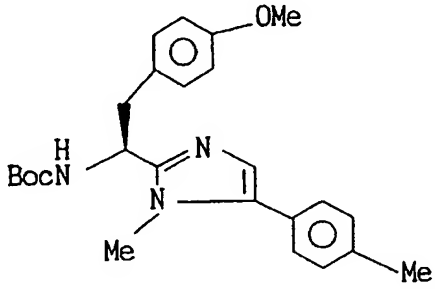
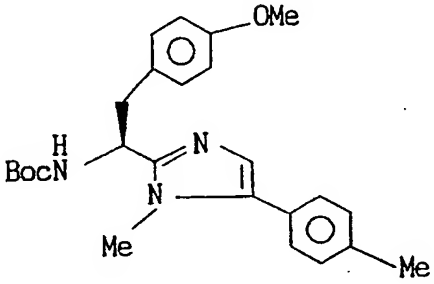
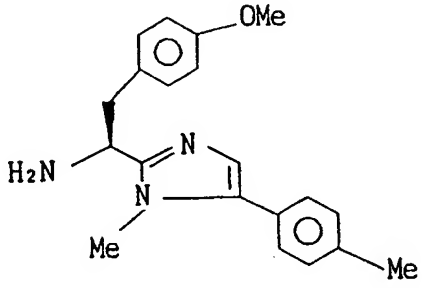
72	
	
73	
	

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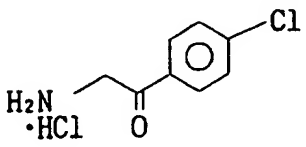
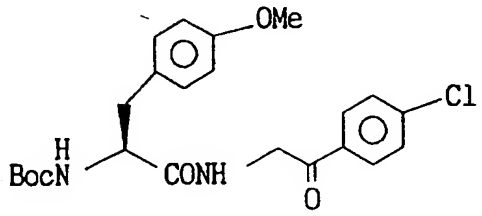
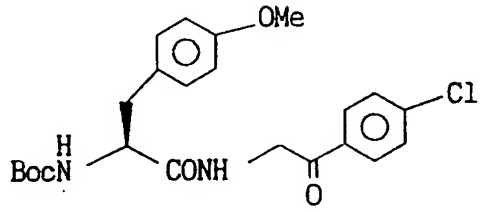
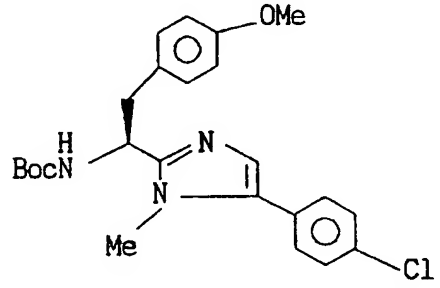
74	
	
75	
	

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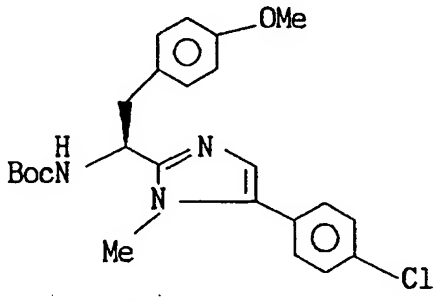
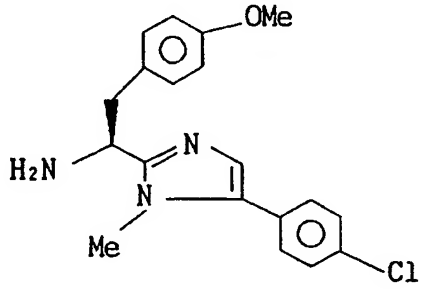
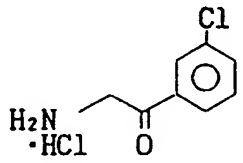
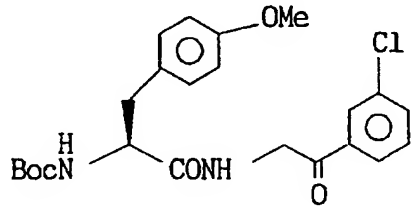
76	
	
77	
	

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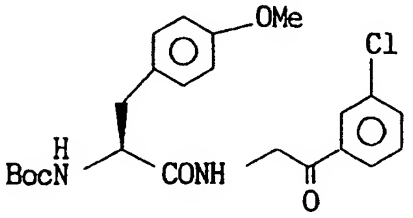
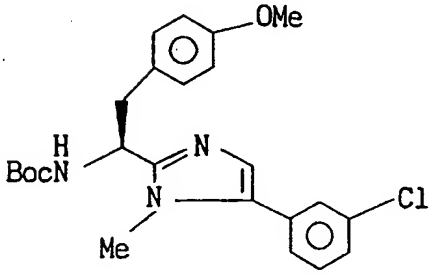
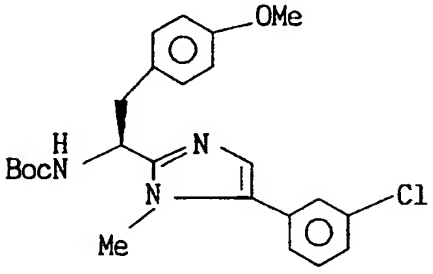
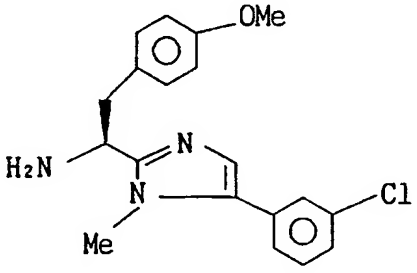
78	
	
79	
	

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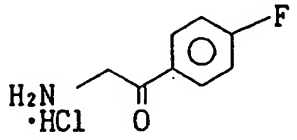
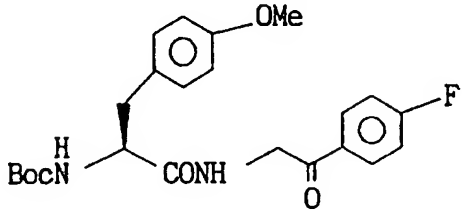
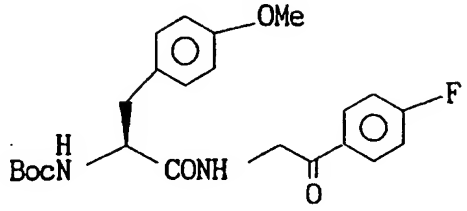
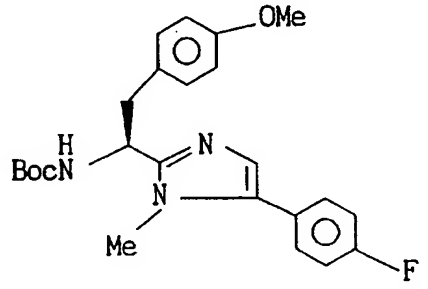
80	
	
81	
	

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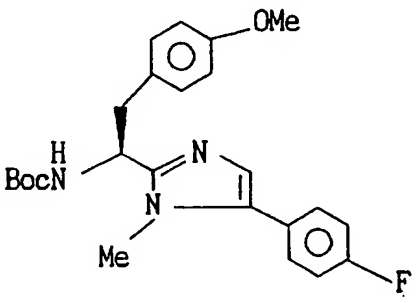
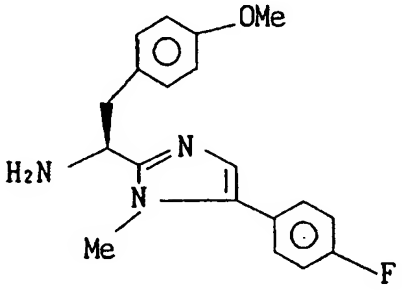
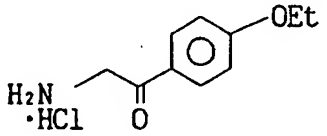
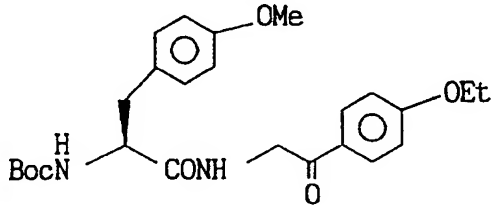
82	
	
83	
	

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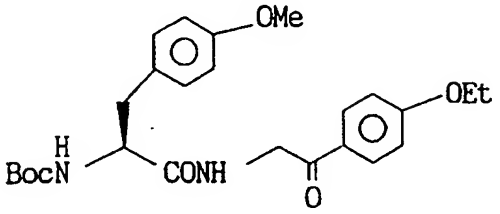
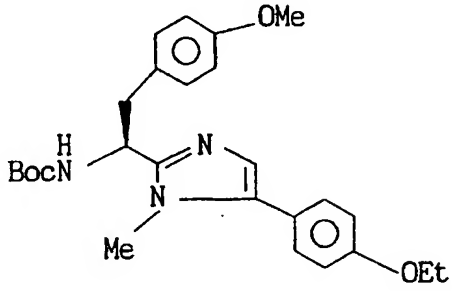
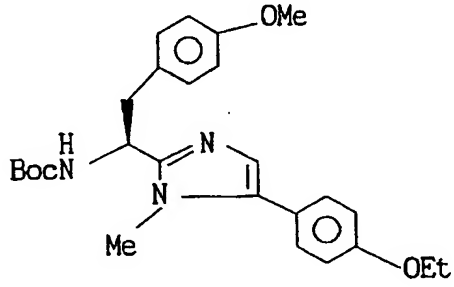
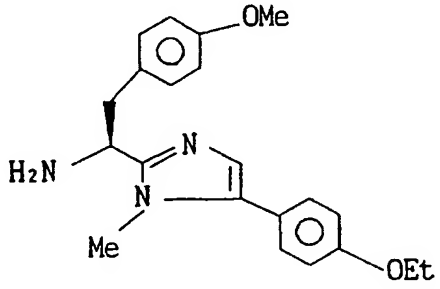
84	
	
85	
	

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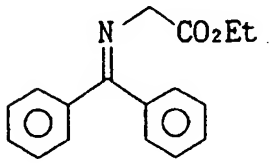
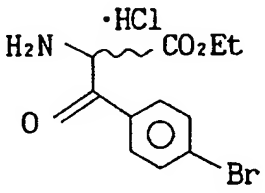
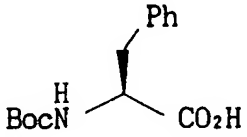
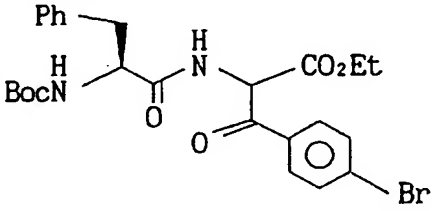
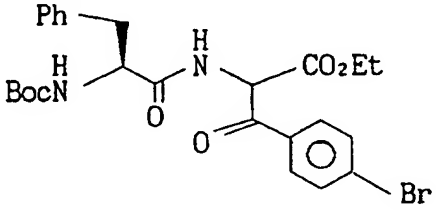
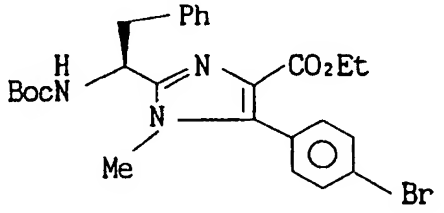
86	
	
87	
	
88	
	

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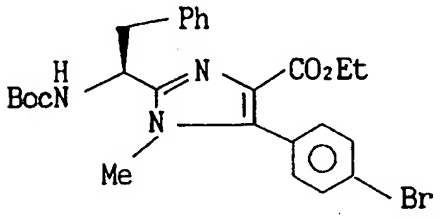
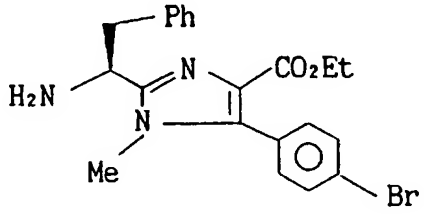
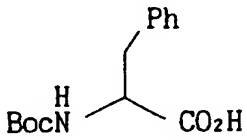
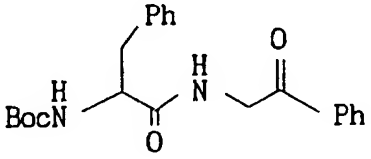
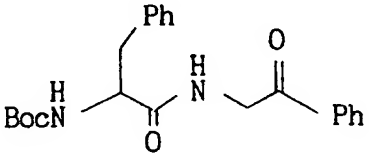
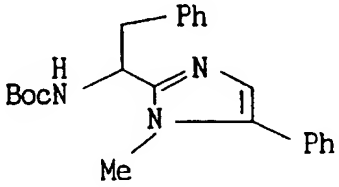
89	
	
90	
	
91	
	

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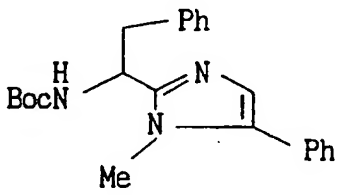
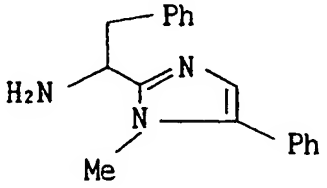
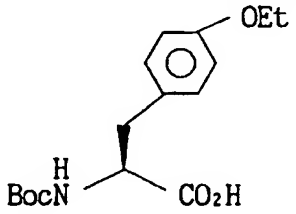
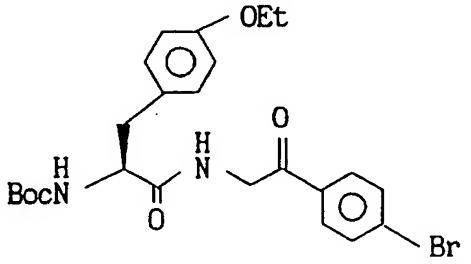
92	
	
93	
	

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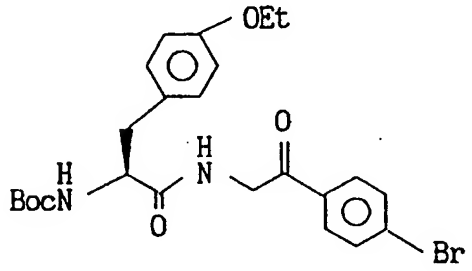
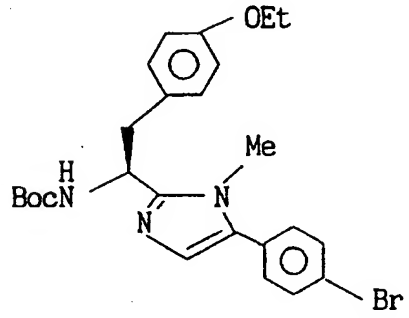
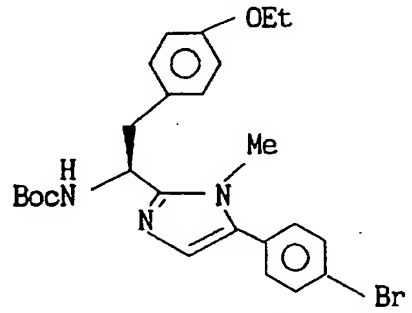
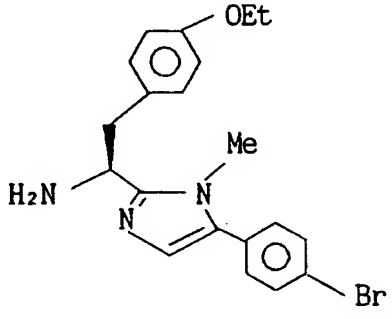
94	
	
95	
	

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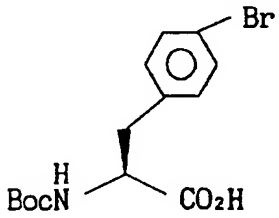
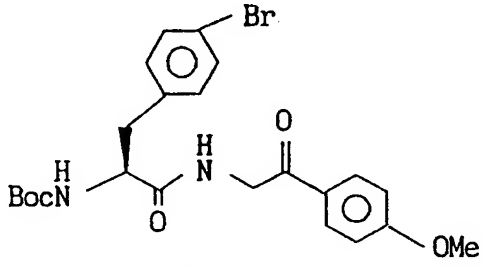
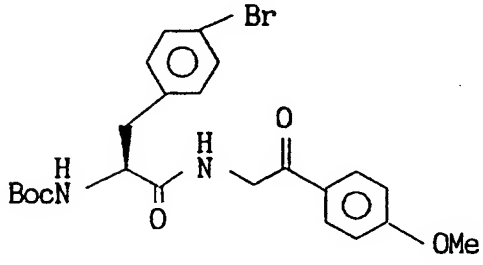
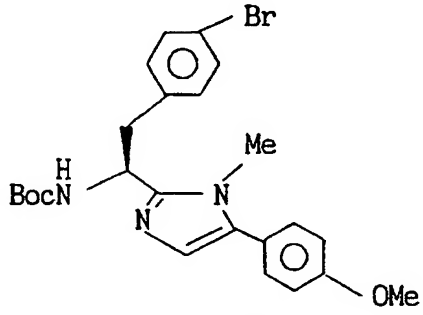
96	
	
97	
	

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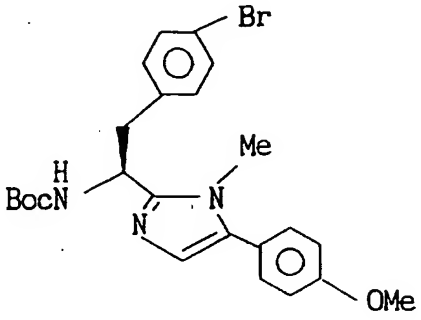
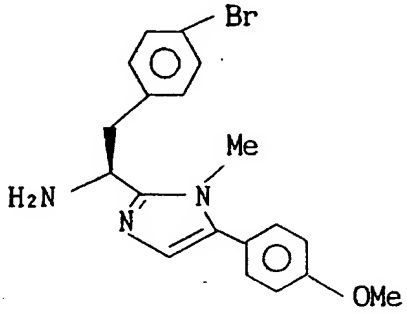
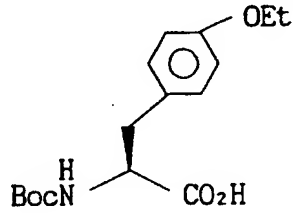
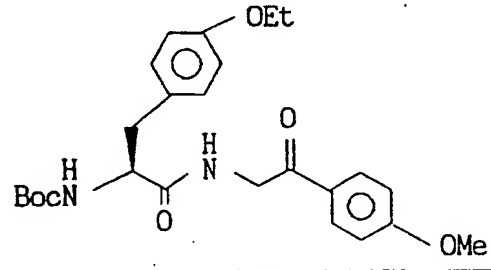
98	
	
99	
	

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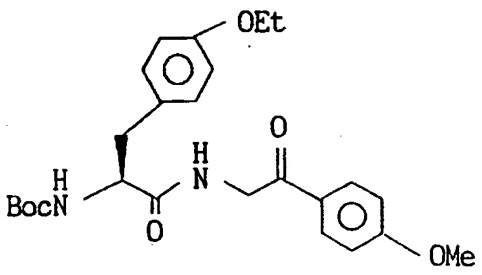
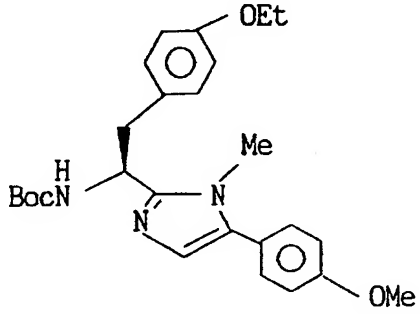
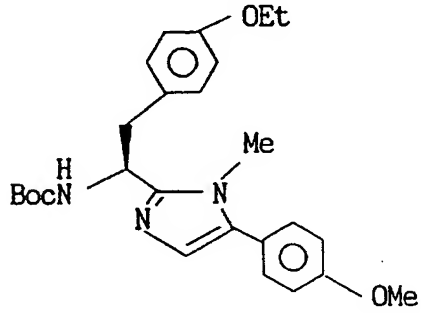
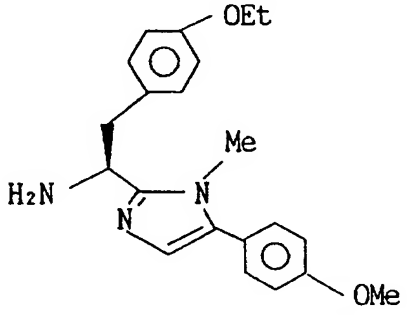
100	
	
101	
	

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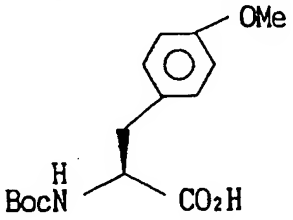
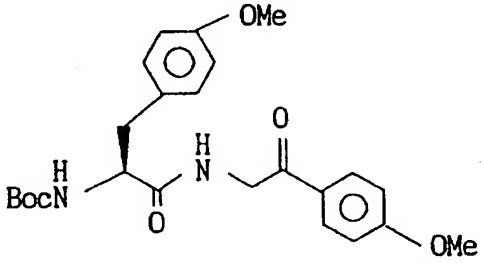
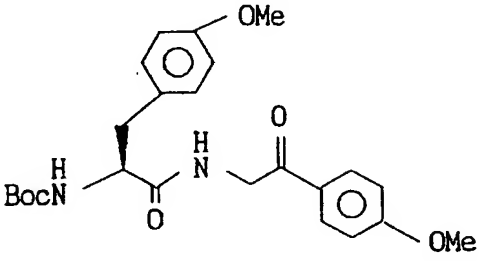
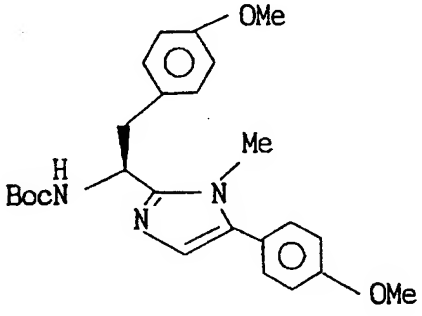
102	
	
103	
	

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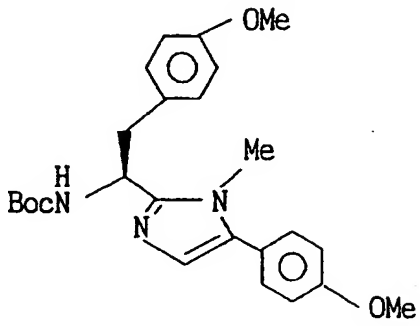
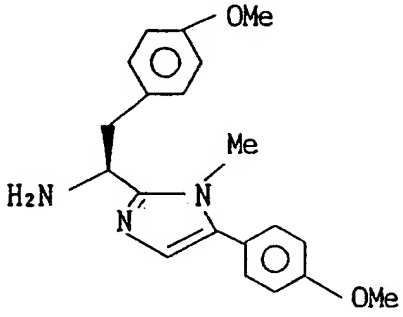
104	
	

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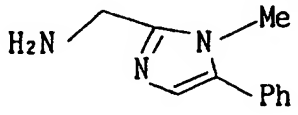
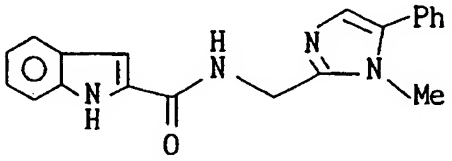
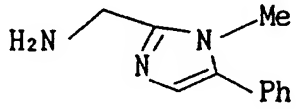
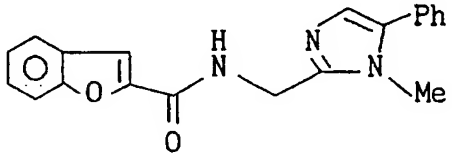
1	
	
2	
	

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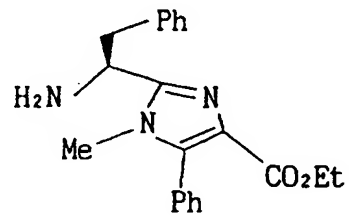
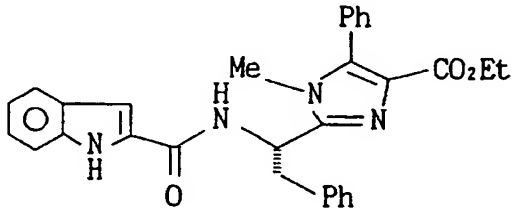
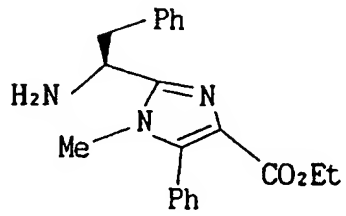
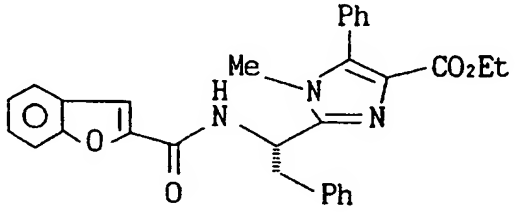
3	
	
4	
	

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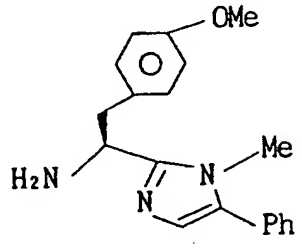
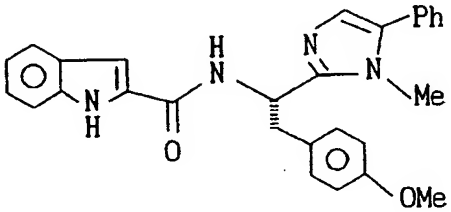
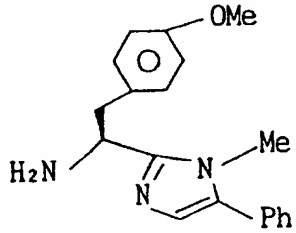
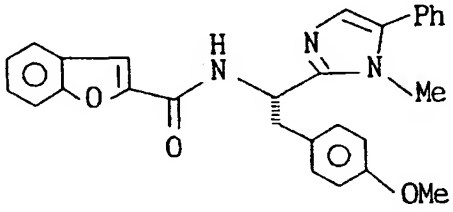
5	
	
6	
	

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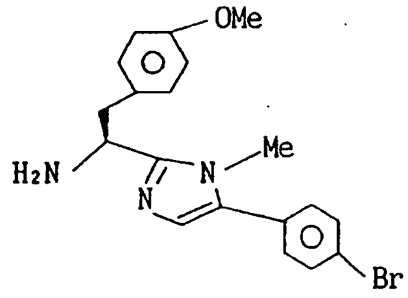
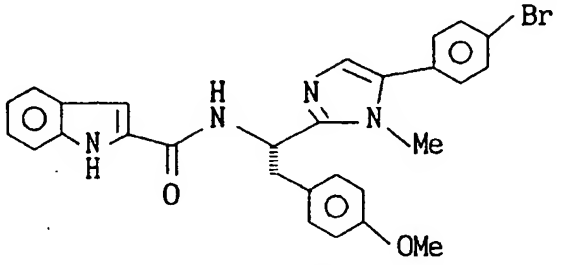
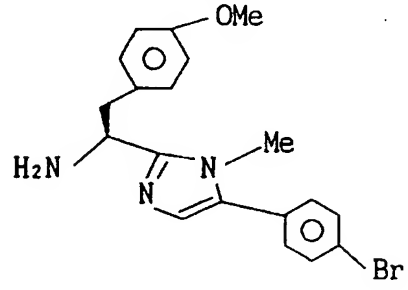
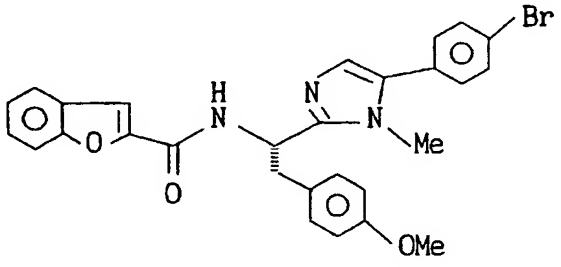
7	
	
8	
	

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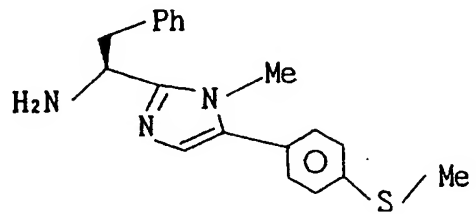
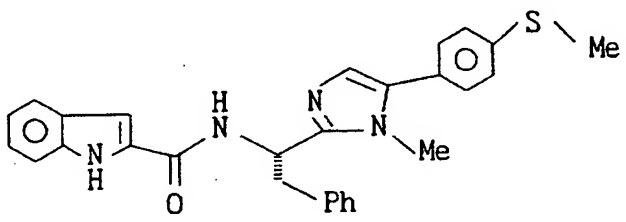
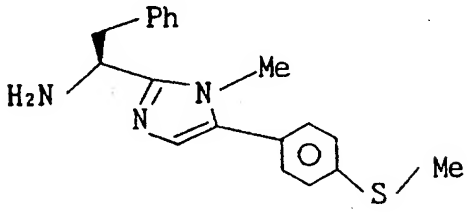
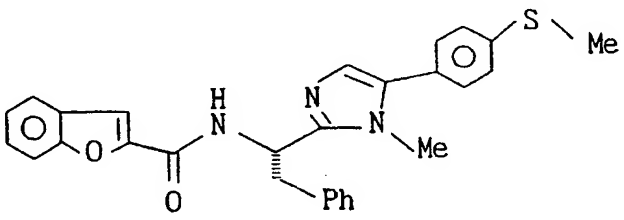
9	
	
10	
	

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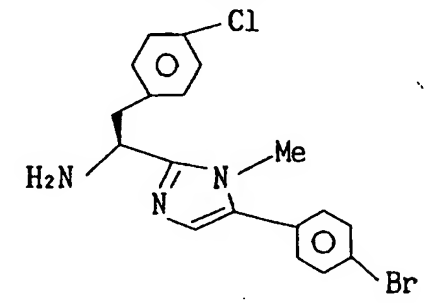
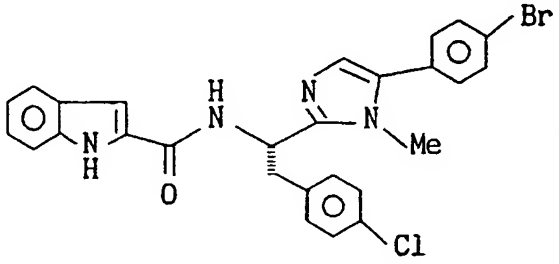
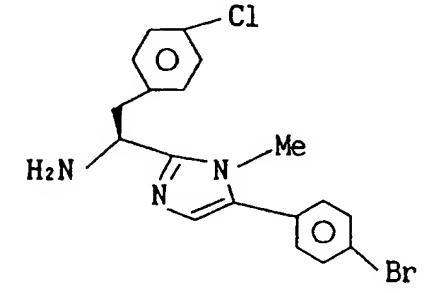
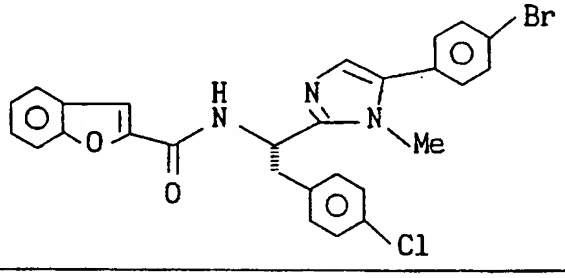
11	
	
12	
	

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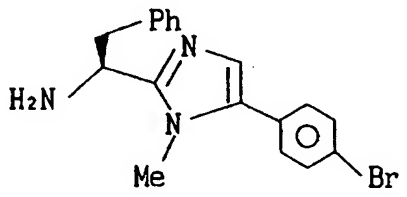
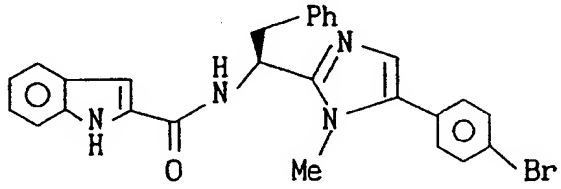
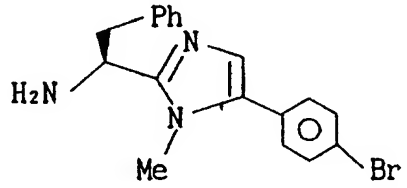
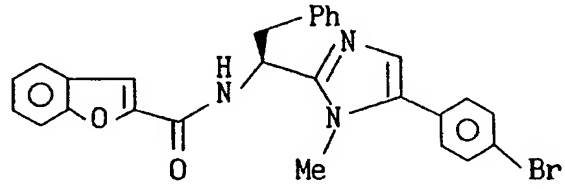
13	
	
14	
	

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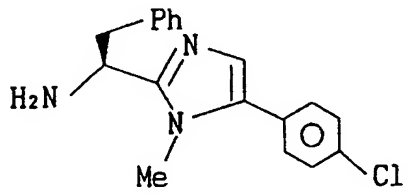
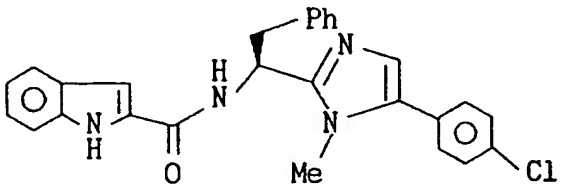
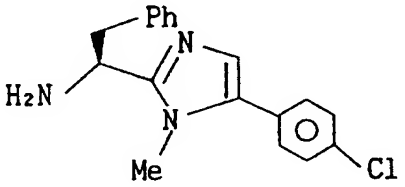
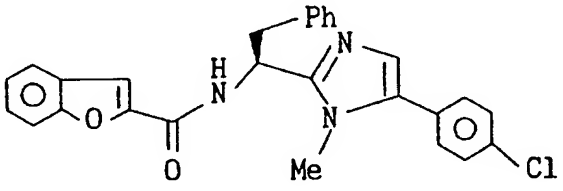
15	
	
16	
	

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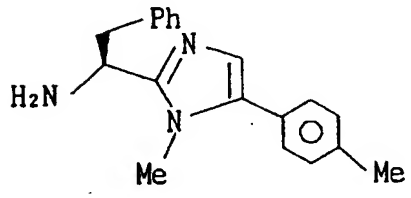
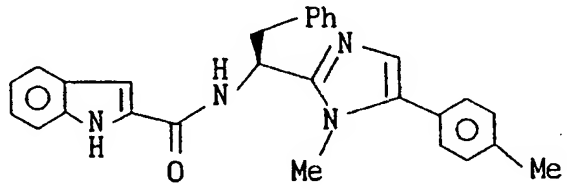
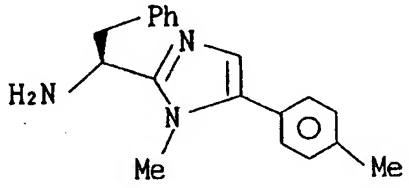
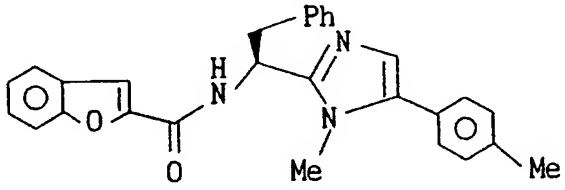
17	
	
18	
	

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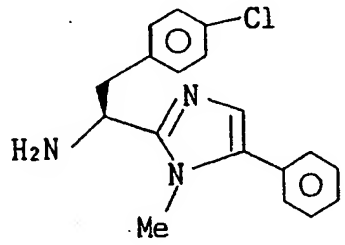
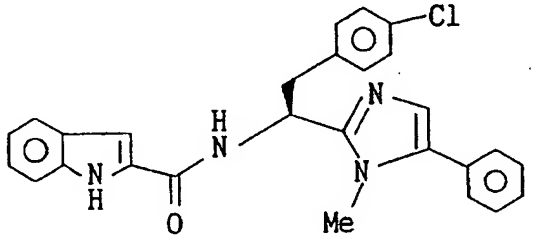
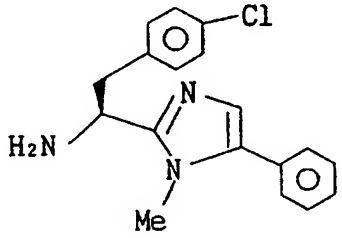
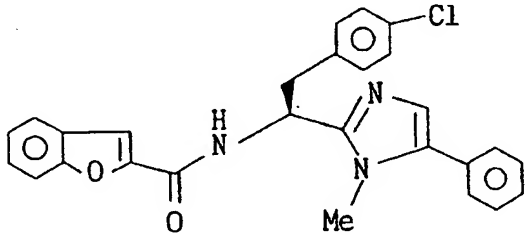
19	
	
20	
	

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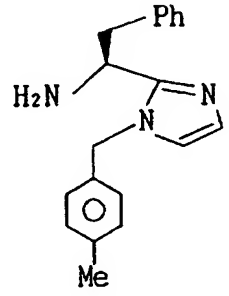
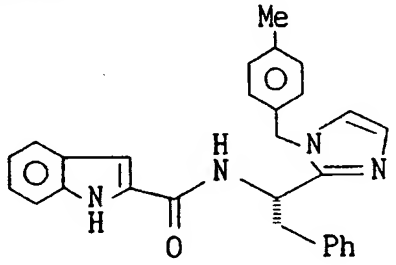
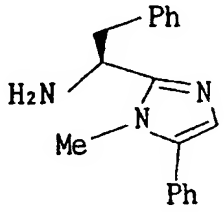
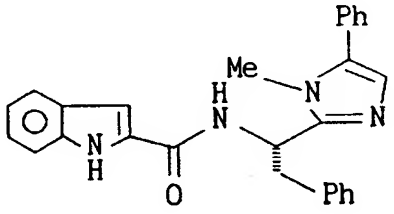
21	
	
22	
	

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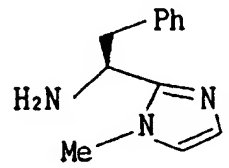
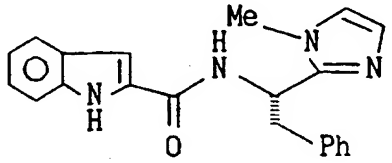
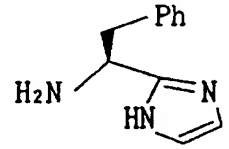
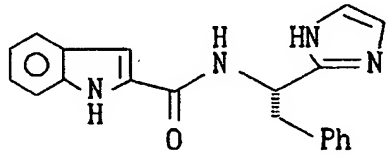
23	
	
24	
	

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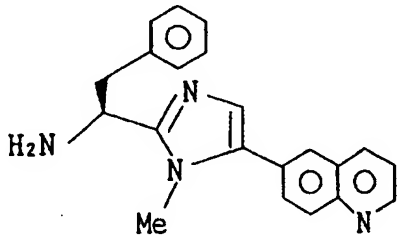
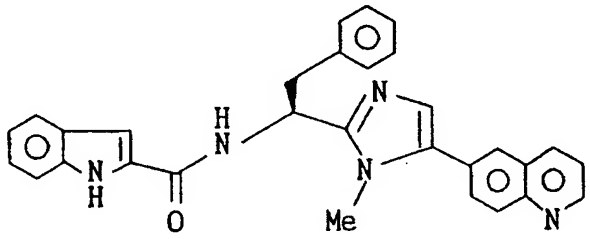
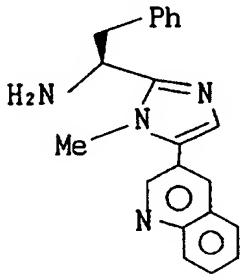
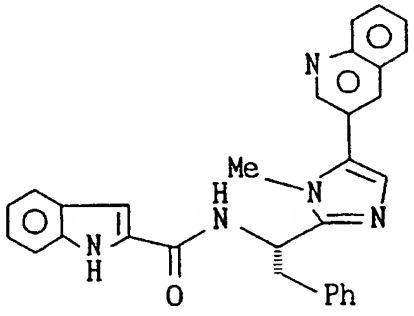
25	
	
26	
	

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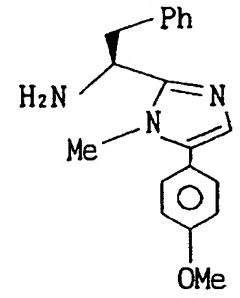
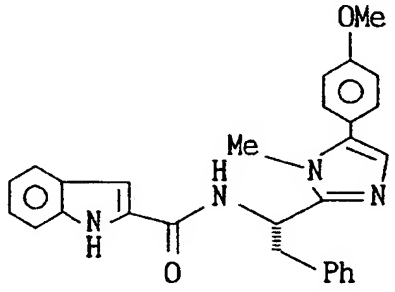
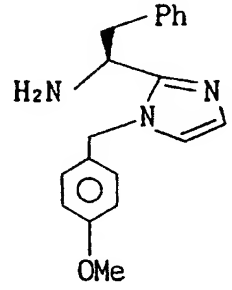
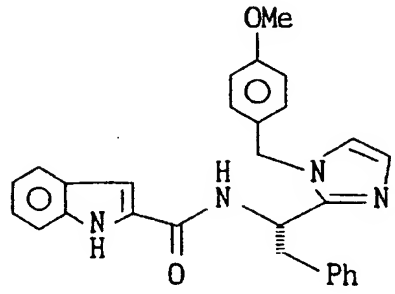
27	
	
28	
	

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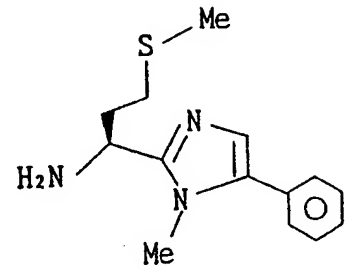
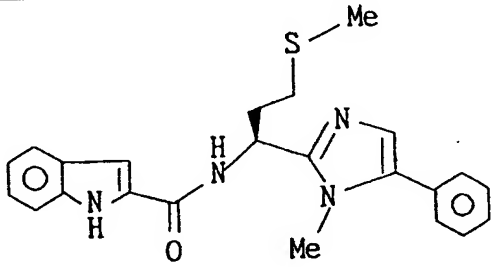
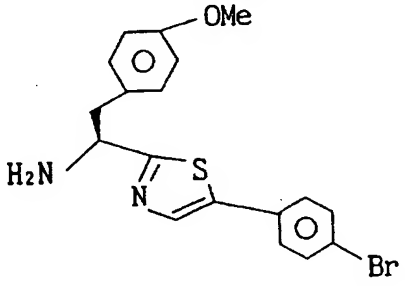
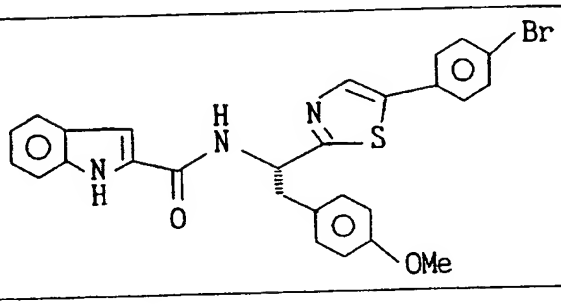
29	
	
30	
	

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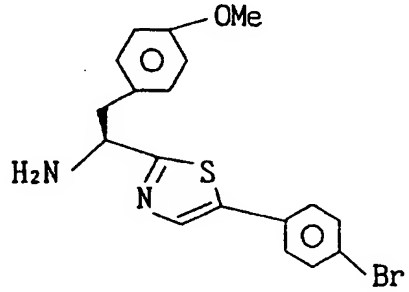
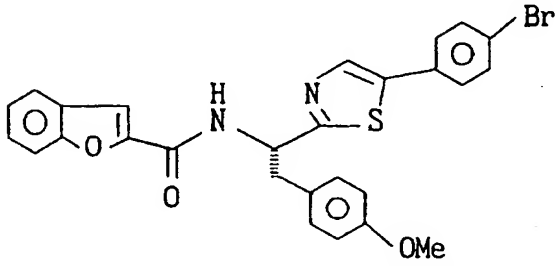
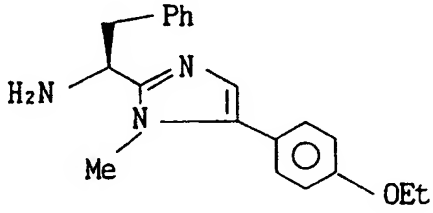
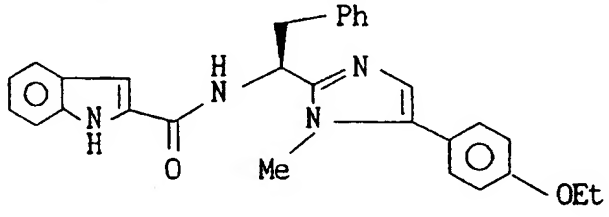
31	
	
32	
	

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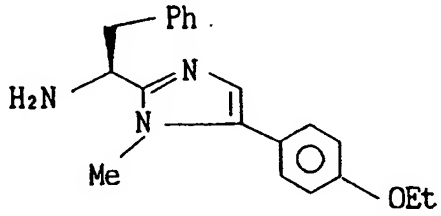
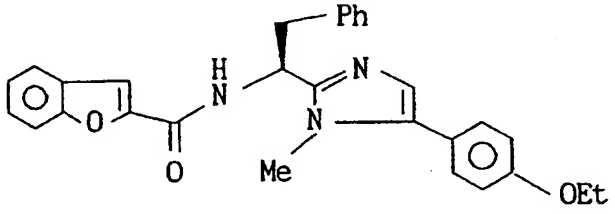
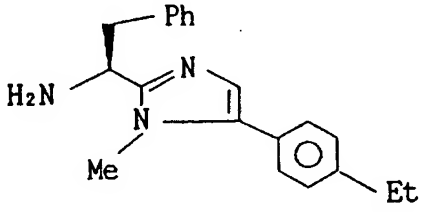
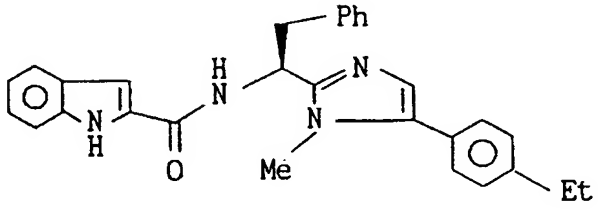
33	
	
34	
	

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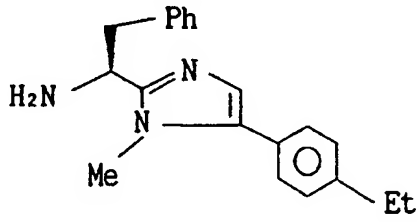
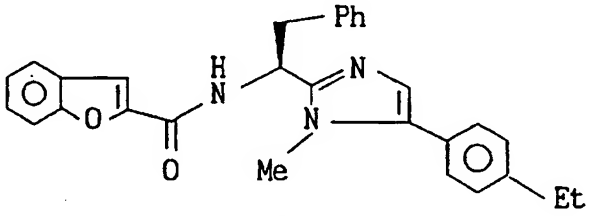
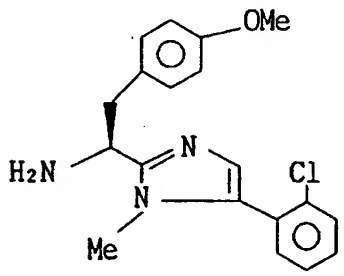
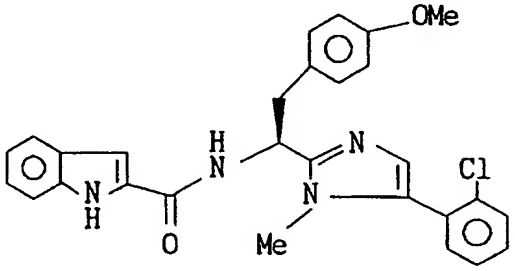
35	
	
36	
	

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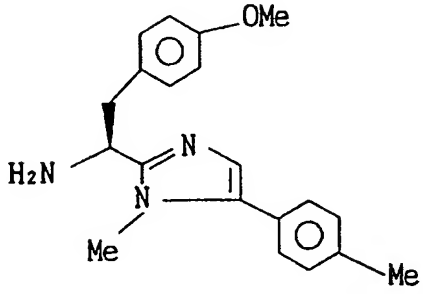
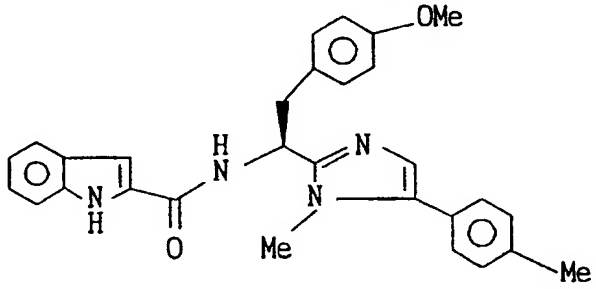
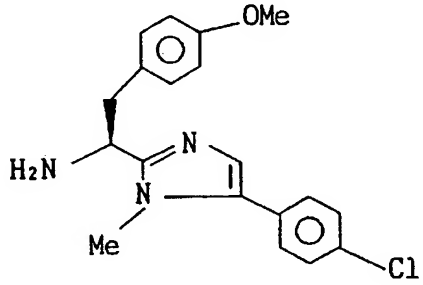
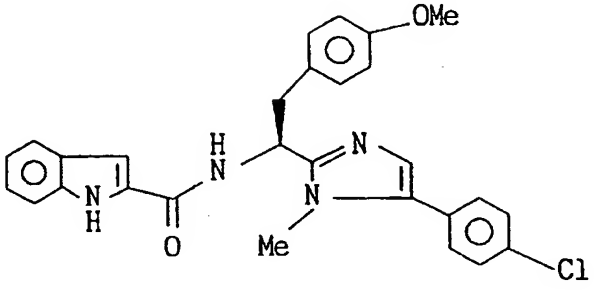
37	
	
38	
	

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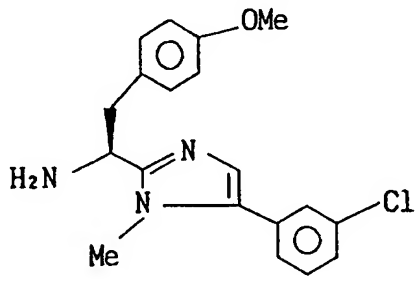
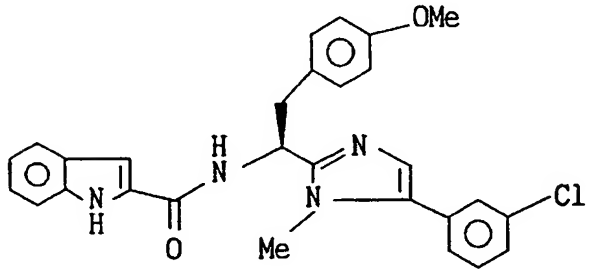
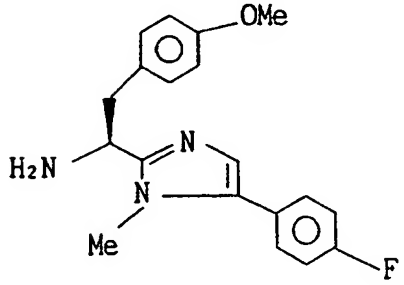
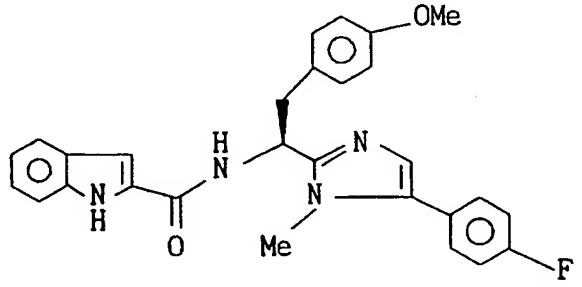
39	
	
40	
	

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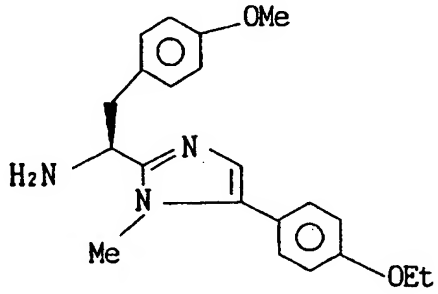
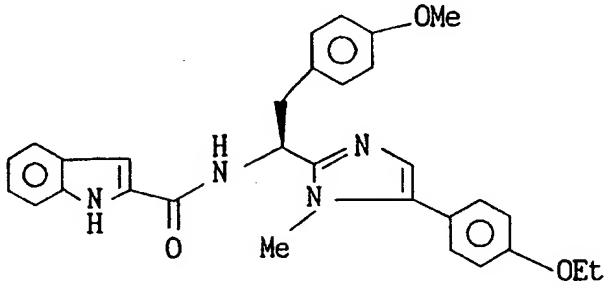
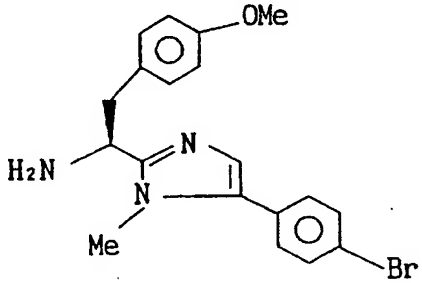
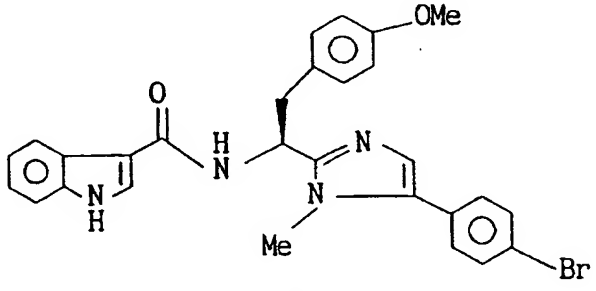
41	
	
42	
	

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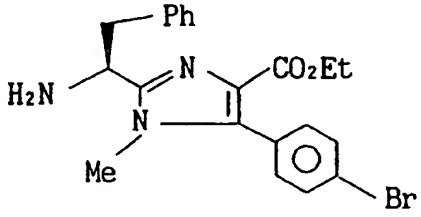
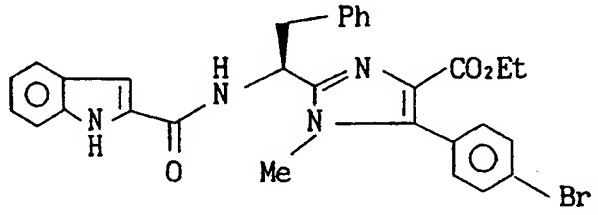
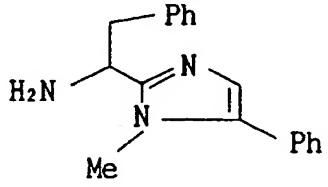
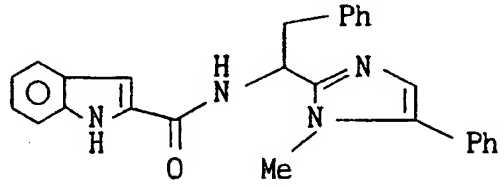
43	
	
44	
	

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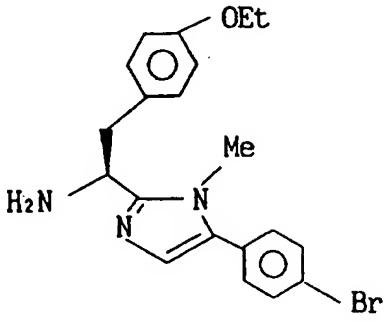
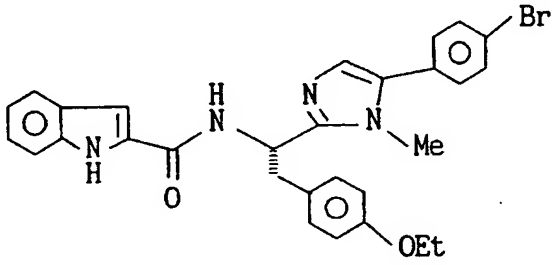
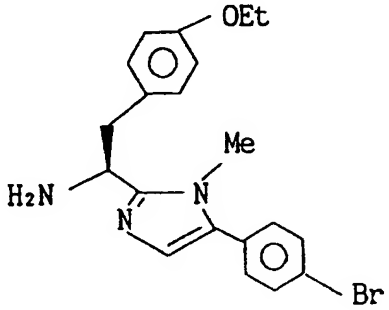
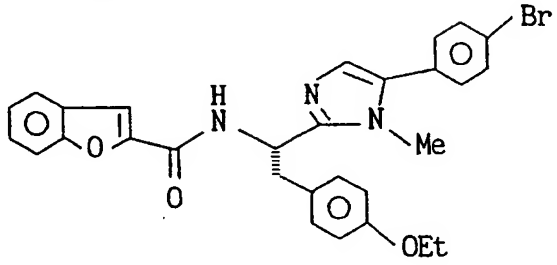
45	
	
46	
	

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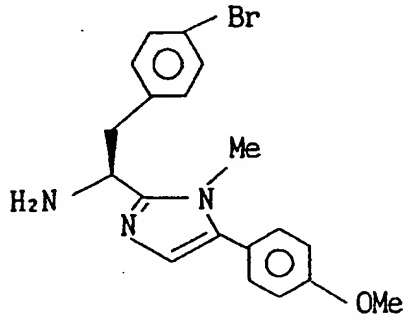
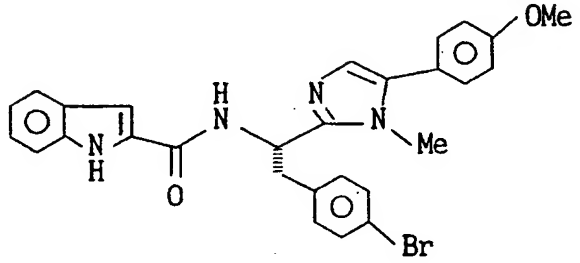
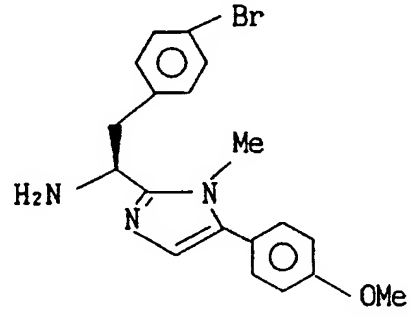
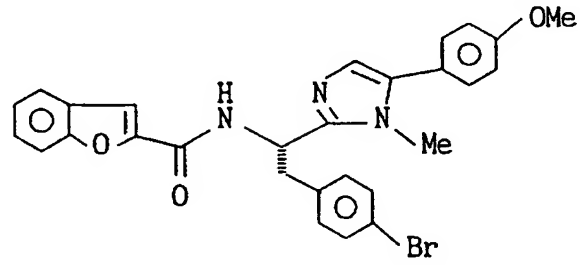
47	
	
48	
	

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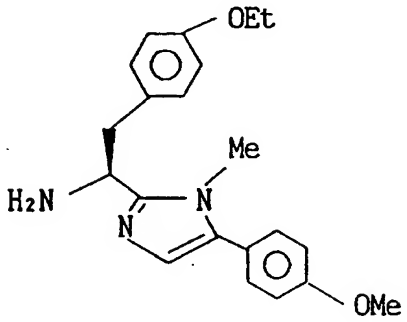
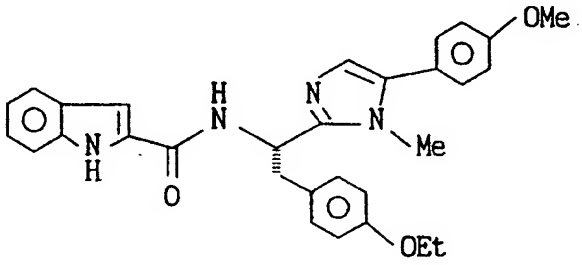
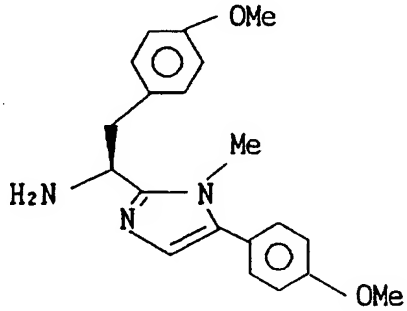
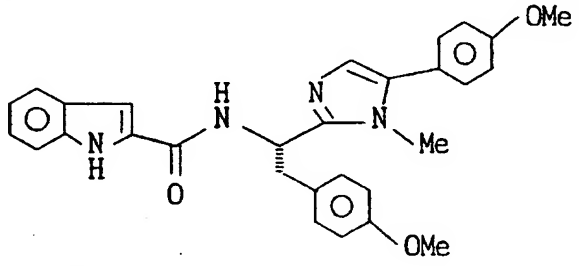
Example No.	Formula
49	
	
50	
	

Preparation 1

To an ice-cooled mixture of N-(tert-butoxycarbonyl)glycine (1.40 g) and 2-aminoacetophenone hydrochloride (1.61 g) in dichloromethane (14 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.49 g). The mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium hydrogencarbonate solution was added to the mixture, and then the mixture was extracted three times with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica gel, chloroform/methanol= 40/1) to give the object compound as white powder (689 mg).

MASS (ESI) (m/z) : 293 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, 300MHz) δ : 1.47(9H,s), 3.92(2H,d,J=5Hz), 4.78(2H,s), 5.13(1H,br s), 7.05(1H,br s), 7.45-7.70(3H,m), 7.92-8.04(2H,m)

Preparation 2

A solution of the starting compound (669 mg) and 40% methylamine (0.7 ml) in a mixture of acetic acid (0.7 ml) and xylene (7 ml) was refluxed for 4 hours in a flask equipped with a Dean-Stark trap. The mixture was concentrated, neutralized with 1N hydroxide solution, and extracted three times with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica gel, chloroform/methanol=50/1) to give the object compound as an oil (445 mg).

MASS (ESI) (m/z) : 288 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, 300MHz) δ : 1.46(9H,s), 3.60(3H,s), 4.48(2H,d,J=5Hz), 5.33(1H,br s), 6.99(1H,s), 7.30-7.52(5H,m)

Preparation 3

The starting compound (430 mg) was dissolved in trifluoroacetic acid (1.5 ml) and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated, made basic with 1N sodium

hydroxide solution and extracted three times with chloroform. The organic layer was dried over magnesium sulfate and filtered. Evaporation of the solvent gave the object compound as an oil (314 mg).

MASS (ESI) (m/z) : 188 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.57(3H,s), 3.98(2H,s), 6.98(1H,s), 7.26-7.50(5H,m)

Preparation 4

To a solution of the starting compound (2.12 g) in tetrahydrofuran (20 ml) was added successively isobutyl chloroformate (1.1 ml) and N-methylmorpholine (0.9 ml) at -25℃, and the mixture was stirred at the temperature for 5 minutes. The above mixture was added to a solution of dl-2-benzoylglycine ethyl ester hydrochloride (2.05 g) and N-methylmorpholine (0.9 ml) in tetrahydrofuran (5 ml) at -20℃, and the mixture was allowed to warm to room temperature for 2 hours. Water was added to the mixture, and the mixture was extracted three times with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate=3/1) to give the object compound as an oil (2.36 g).

MASS (ESI) (m/z) : 455 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.13(3H,t,J=7Hz), 1.41(9H,s), 2.95-3.21(2H,m), 4.13(2H,q,J=7Hz), 4.38-4.60(1H,m), 4.83-5.05(1H,m), 6.02-6.20(1H,m), 7.10-7.37(6H,m), 7.42-7.71(3H,m), 8.01-8.18(2H,m)

Preparation 5

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 450 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.12(3H,t,J=7Hz), 1.40(9H,s), 2.68(3H,s), 3.08-3.42(2H,m), 4.21(2H,q,J=7Hz), 4.89-5.05(1H,m), 5.77(1H,br d,J=8Hz), 6.96-7.48(10H,m)

Preparation 6

The object compound was obtained according to a similar manner to that of Preparation 3.

MASS (ESI) (m/z) : 350 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.08(3H,t,J=7Hz), 2.80(3H,s), 3.21-3.48(2H,m), 4.15(2H,q,J=7Hz), 4.25-4.72(3H,m), 7.00-7.48(10H,m)

Preparation 7

The object compound was obtained according to a similar manner to that of Preparation 1.

MASS (ESI) (m/z) : 413 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.41(9H,s), 3.05(2H,d,J=6Hz), 3.75(3H,s), 4.43(1H,br s), 4.58-4.81(2H,m), 5.05(1H,br s), 6.81(2H,d,J=8Hz), 6.91(1H,br s), 7.12(2H,d,J=8Hz), 7.42-7.68(3H,m), 7.95(2H,d,J=7Hz)

Preparation 8

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 408 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.42(9H,s), 3.00-3.33(2H,m), 3.02(3H,s), 3.77(3H,s), 4.89-5.04(1H,m), 5.63(1H,d,J=8Hz), 6.76(2H,d,J=8Hz), 6.94(2H,d,J=8Hz), 7.02(1H,s), 7.18-7.45(5H,m)

Preparation 9

To a solution of the starting compound (3.10 g) in methanol (15 ml) was added concentrated hydrochloric acid (3 ml), and the mixture was heated to 50°C for 2 hours. The mixture was concentrated, made basic with a 1N sodium hydroxide solution, and extracted three times with chloroform. The organic layer was dried over magnesium sulfate, and filtered. Evaporation of the solvent gave the object compound(2.35 g).

MASS (ESI) (m/z) : 308 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.02-3.22(2H,m), 3.21(3H,s),
3.78(3H,s), 4.11(1H,t,J=7Hz), 6.81(2H,d,J=8Hz),
6.99(2H,d,J=8Hz), 7.04(1H,s), 7.21-7.48(5H,m)

Preparation 10

The object compound was obtained according to a similar manner to that of Preparation 1.

MASS (ESI) (m/z) : 491,493 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.41(9H,s), 3.04(2H,d,J=6Hz),
3.75(3H,s), 4.42(1H,br s), 4.54-4.77(2H,m), 5.00(1H,br s),
6.81(2H,d,J=8Hz), 6.85(1H,br s), 7.12(2H,d,J=8Hz),
7.63(2H,d,J=7Hz), 7.80(2H,d,J=7Hz)

Preparation 11

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 486,488 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.41(9H,s), 3.00(3H,s),
3.01-3.32(2H,m), 3.76(3H,s), 4.88-5.02(1H,m),
5.57(1H,d,J=8Hz), 6.76(2H,d,J=8Hz), 6.88-7.18(5H,m),
7.51(2H,d,J=8Hz)

Preparation 12

The object compound was obtained according to a similar manner to that of Preparation 9.

MASS (ESI) (m/z) : 386,388 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.02-3.18(2H,m), 3.20(3H,s),
3.78(3H,s), 4.12(1H,t,J=7Hz), 6.81(2H,d,J=8Hz),
6.98(2H,d,J=8Hz), 7.03(1H,s), 7.15(2H,d,J=8Hz),
7.52(2H,d,J=8Hz)

Preparation 13

The object compound was obtained according to a similar manner to that of Preparation 1.

MASS (ESI) (m/z) : 429 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.41(9H,s), 2.52(3H,s),

2.99-3.21(2H,m), 4.48(1H,br s), 4.53-4.79(2H,m),
5.03(1H,br s), 6.90(1H,br s), 7.13-7.25(7H,m),
7.83(2H,d,J=8Hz)

Preparation 14

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 424 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.40(9H,s), 2.50(3H,s),
2.94(3H,s), 3.00-3.40(2H,m), 4.90-5.10(1H,m),
5.59(1H,br d,J=8Hz), 6.95-7.35(10H,m)

Preparation 15

The object compound was obtained according to a similar manner to that of Preparation 9.

MASS (ESI) (m/z) : 324 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 2.50(3H,s), 3.08-3.27(2H,m),
3.17(3H,s), 4.16(1H,t,J=7Hz), 7.03(1H,s), 7.05-7.35(9H,m)

Preparation 16

The object compound was obtained according to a similar manner to that of Preparation 1.

MASS (ESI) (m/z) : 495, 497 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.40(9H,s), 2.98-3.20(2H,m),
4.47(1H,m), 4.55-4.78(2H,m), 5.10(1H,br d,J=8Hz),
7.01(1H,br s), 7.14(2H,d,J=8Hz), 7.25(2H,d,J=8Hz),
7.64(2H,d,J=8Hz), 7.81(2H,d,J=8Hz)

Preparation 17

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 490, 492 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.39(9H,s), 3.12(3H,s),
3.13-3.22(2H,m), 4.91-5.08(1H,m), 5.47(1H,br d,J=9Hz),
6.90-7.30(7H,m), 7.52(2H,d,J=8Hz)

Preparation 18

The object compound was obtained according to a similar manner to that of Preparation 9.

MASS (ESI) (m/z) : 390, 392 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.02-3.26(2H,m), 3.27(3H,s), 4.11(1H,t,J=7Hz), 7.02(2H,d,J=8Hz), 7.03(1H,s), 7.15(2H,d,J=8Hz), 7.22(2H,d,J=8Hz), 7.53(2H,d,J=8Hz)

Preparation 19

The object compound was obtained according to a similar manner to that of Preparation 1.

amorphous solid

MASS : 461 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.39(9H,s), 3.00-3.20(2H,m), 4.40-4.78(3H,m), 5.03(1H,bs), 6.89(1H,bs), 7.19-7.38(5H,m), 7.63(2H,d,J=8Hz), 7.82(2H,d,J=8Hz)

Preparation 20

The object compound was obtained according to a similar manner to that of Preparation 2.

mp : 162-164℃

MASS : 456 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.41(9H,s), 2.97(3H,s), 3.11(1 x 1/3H,d,J=8Hz), 3.15(1 x 2/3H,d,J=8Hz), 3.31(1 x 2/3H,d,J=8Hz), 3.35(1 x 1/3H,d,J=8Hz), 4.91-5.08(1H,m), 5.59(1H,d,J=8Hz), 6.99-7.07(3H,m), 7.09(2H,d,J=8Hz), 7.18-7.23(3H,m), 7.51(2H,d,J=8Hz)

Preparation 21

The object compound was obtained according to a similar manner to that of Preparation 3.

oil

MASS : 356 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 3.10-3.25(2H,m), 3.20(3H,s), 4.17(1H,t,J=8Hz), 7.05(1H,s), 7.10(2H,d,J=8Hz), 7.14(2H,d,J=8Hz), 7.20-7.32(3H,m), 7.53(2H,d,J=8Hz)

Preparation 22

The object compound was obtained according to a similar manner to that of Preparation 1.

amorphous solid

MASS : 417 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.40(9H,s), 3.11(2H,d,J=8Hz), 4.40-4.60(1H,m), 4.60-4.78(2H,m), 5.00(1H,bs), 6.84(1H,bs), 7.17-7.36(5H,m), 7.49(2H,d,J=8Hz), 7.90(2H,d,J=8Hz)

Preparation 23

The object compound was obtained according to a similar manner to that of Preparation 2.

amorphous solid

MASS : 412 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.41(9H,s), 2.92(3H,s), 3.00-3.20(1H,m), 3.24-3.40(1H,m), 5.00(1H,q,J=8Hz), 5.59(1H,d,J=8Hz), 7.00-7.10(3H,m), 7.14(2H,d,J=8Hz), 7.18-7.30(3H,m), 7.37(2H,d,J=8Hz)

Preparation 24

The object compound was obtained according to a similar manner to that of Preparation 3.

oil

MASS : 312 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 3.10-3.28(2H,m), 3.18(3H,s), 4.10-4.24(1H,m), 7.08(2H,d,J=8Hz), 7.11(1H,s), 7.21(2H,d,J=8Hz), 7.22-7.33(3H,m), 7.39(2H,d,J=8Hz)

Preparation 25

The object compound was obtained according to a similar manner to that of Preparation 1.

mp : 135-139℃

MASS : 397 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.41(9H,s), 2.41(3H,s), 3.00-3.20(2H,m), 4.50(1H,d,J=5Hz), 4.57-4.78(2H,m), 5.07(1H,d,J=5Hz),

6.91(1H,s), 7.18-7.33(7H,m), 7.83(2H,d,J=8Hz)

Preparation 26

The object compound was obtained according to a similar manner to that of Preparation 2.

mp : 131-133℃

MASS : 392 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.39(9H,s), 2.38(3H,s), 2.97(3H,s), 3.11(1 x 1/3H,d,J=8Hz), 3.17(1 x 2/3H,d,J=8Hz), 3.31(1 x 2/3H,d,J=8Hz), 3.36(1 x 1/3H,d,J=8Hz), 4.93-5.08(1H,m), 5.59(1H,d,J=8Hz), 7.00(1H,s), 7.01-7.09(2H,m), 7.09-7.16(2H,m), 7.16-7.28(5H,m)

Preparation 27

The object compound was obtained according to a similar manner to that of Preparation 3.

oil

MASS : 292 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 2.37(3H,s), 3.10-3.27(2H,m), 3.19(3H,s), 4.17(1H,t,J=8Hz), 7.01(1H,s), 7.09(2H,d,J=8Hz), 7.12-7.33(7H,m)

Preparation 28

To an ice-cooled mixture of the starting compound (599 mg), 2-aminoacetophenone hydrochloride (362 mg) and 1-hydroxybenzotriazole (270 mg) in dichloromethane (6 ml) was added 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide (349 mg). The mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium hydrogencarbonate solution was added to the mixture, and then the mixture was extracted three times with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by column chromatography (silica gel, chloroform/methanol=70/1) to give the object compound (823 mg).

MASS (ESI) (m/z) : 417 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.41(9H,s), 2.96-3.20(2H,m), 4.47(1H,m), 4.70(2H,AB of ABX,J_{AB}=15Hz), 5.01(1H,br s), 6.92(1H,br s), 7.13(2H,d,J=8Hz), 7.24(2H,d,J=8Hz), 7.41-7.68(3H,m), 7.88-8.00(2H,m)

Preparation 29

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 412 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.40(9H,s), 3.13(3H,s), 3.15-3.32(2H,m), 4.92-5.07(1H,m), 5.58(1H,br d,J=8Hz), 6.93-7.55(10H,m)

Preparation 30

The object compound was obtained according to a similar manner to that of Preparation 3.

MASS (ESI) (m/z) : 312 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.06-3.25(2H,m), 3.24(3H,s), 4.17(1H,t,J=7Hz), 6.98-7.50(10H,m)

Preparation 31

The starting compound (1.1 g) and glyoxal trimeric dihydrate (930 mg) were stirred in methanol (7 ml) at -10℃. Ammonia was bubbled through the solution for 5 minutes and the mixture was stirred at -10℃ for 1 hour. The mixture was allowed to warm to room temperature over 18 hours, then poured into water, and extracted twice with dichloromethane. The combined extracts was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with a dichloromethane-methanol gradient (20:1 and 10:1) as eluent to give the object compound as an off-white solid (698.6 mg).

mp : 180.5-184℃

MASS : 288 $(M+H)^+$

^{1}H-NMR ($CDCl_3$) δ : 1.40(9H,s), 3.29(2H,d,J=7.5Hz), 4.90(1H,q,J=7.5Hz), 5.25(1H,bd,J=7.5Hz), 6.89(1H,bs),

6.99(1H,bs), 7.12(2H,d,J=7.5Hz), 7.18-7.30(3H,m),
9.78(1H,bs)

Preparation 32

To a precooled solution of the starting compound (500 mg) in N,N-dimethylformamide (5 ml) was added 85% potassium hydroxide powder (115 mg). After the mixture was stirred for 1 hour on an ice bath, α-chloro-p-xylene (230.4 μl) was added dropwise to the reaction mixture. The resulting suspension was stirred at 5℃ for 14 hours, then poured into water, and extracted with chloroform. The organic layer was washed twice with water and a saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was washed with diethyl ether to give the object compound as a colorless solid (418.3 mg).

mp : 157-158.5℃

MASS : 392 $(M+H)^+$

^{1}H-NMR ($CDCl_3$) δ : 1.36(9H,s), 2.30(3H,s), 3.19(2H,m),
4.63(1H,d,J=16.0Hz), 4.71(1H,d,J=16.0Hz), 5.01(1H,m),
5.32(1H,m), 6.63(1H,s), 6.77(2H,d,J=7.5Hz), 6.98-7.23(8H,m)

Preparation 33

The object compound was obtained according to a similar manner to that of Preparation 3.

colorless oil

MASS : 292 $(M+H)^+$

^{1}H-NMR ($CDCl_3$) δ : 2.31(3H,s), 3.02(1H,dd,J=13.5 and 7.5Hz),
3.12(1H,dd,J=13.5 and 7.5Hz), 4.06(1H,t,J=7.5Hz),
4.76(1H,d,J=14.5Hz), 4.83(1H,d,J=14.5Hz), 6.71(1H,s),
6.86(2H,d,J=7.5Hz), 6.99-7.04(3H,m), 7.10(2H,d,J=7.5Hz),
7.20-7.30(3H,m)

Preparation 34

The object compound was obtained according to a similar manner to that of Preparation 1.

white crystals

mp : 134-135℃

MASS (ESI) (m/z) : 383 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, 300MHz) δ : 1.41(9H,s), 3.00-3.22(2H,m),
4.47(1H,m), 4.69(2H,AB of ABX, J_{AB}=19Hz),
5.03(1H,br s), 6.90(1H,br s), 7.16-7.68(8H,m),
7.95(2H,d,J=8Hz)

Preparation 35

The object compound was obtained according to a similar manner to that of Preparation 2.

white crystals

mp : 130-131℃

MASS (ESI) (m/z) : 378 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, 300MHz) δ : 1.41(9H,s), 2.96(3H,s),
3.06-3.20(1H,m), 3.28-3.40(1H,m), 4.92-5.06(1H,m),
5.57(1H,br d,J=9Hz), 7.00-7.43(11H,m)

Preparation 36

The object compound was obtained according to a similar manner to that of Preparation 3.

white powder

MASS (ESI) (m/z) : 278 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, 300MHz) δ : 3.10-3.28(2H,m), 3.18(3H,s),
4.16(1H,t,J=7Hz), 7.05(1H,s), 7.07-7.45(10H,m)

Preparation 37

The starting compound (600 mg) was heated at 40℃ for 2 hours in methyl iodide (10 ml). The reaction mixture was evaporated, and the residue was suspended in an aqueous sodium carbonate solution. The mixture was extracted with chloroform. The organic layer was washed successively with water and a saturated sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel with a chloroform-methanol (20:1) as eluent to give the object compound as a pale yellow oily solid (376.5 mg).

mp : 116-119℃

MASS (ESI) (m/z) : 302 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.40(9H,s), 3.05(3H,s),
3.10(1H,dd,J=14.5, 9.0Hz), 3.29(1H,dd,J=14.5, 4.5Hz),
4.93(1H,m), 5.50(1H,br d,J=7.5Hz), 6.63(1H,s),
6.95-7.02(3H,m), 7.15-7.24(3H,m)

Preparation 38

The object compound was obtained according to a similar manner to that of Preparation 3.

yellow oil

MASS (ESI) (m/z) : 202 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.09(1H,dd,J=14.5, 7.5Hz),
3.13(1H,dd,J=14.5, 7.5Hz), 3.23(3H,s), 4.12(1H,t,J=7.5Hz),
6.69(1H,s), 6.99(1H,s), 7.03(2H,d,J=7.5Hz), 7.16-7.32(3H,m)

Preparation 39

The object compound was obtained according to a similar manner to that of Preparation 3.

yellow oil

MASS (ESI) (m/z) : 188 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 2.82(1H,dd,J=14.5, 8.5Hz),
3.37(1H,dd,J=14.5, 2.5Hz), 4.35(1H,dd,J=8.5, 2.5Hz),
6.99(2H,s), 7.12(2H,d,J=7.5Hz), 7.20-7.34(4H,m)

Preparation 40

A mixture of 6-acetylquinoline (2.0 g), hydroxylamine hydrochloride (1.0 g) and sodium carbonate (1.7 g) in ethanol (20 ml) was refluxed for 1 hour. After cooling to room temperature, water was added to the mixture. The precipitate was collected and washed with diethyl ether to give the object compound as a pale yellow solid (1.7 g).

mp : 170-173℃

MASS (ESI) (m/z) : 187 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 2.43(3H,s), 7.44(1H,dd,J=7.5, 4.5Hz),

8.00(1H,s), 8.16-8.23(3H,m), 8.94(1H,d,J=4.5Hz), 9.46(1H,s)

Preparation 41

To a solution of the starting compound (1.50 g) in pyridine (15 ml) cooled to 0℃ was added p-toluenesulfonyl chloride (1.84 g) with stirring under an atmosphere of nitrogen, and the mixture was stirred at 0℃ for 9 hours. After the reaction mixture was poured into ice-water, the precipitate was collected and washed successively with water and 2-propanol to give the object compound as a pale brown solid (1.62 g).

mp : 119.5-121℃

MASS (ESI) (m/z) : 341 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 2.43(3H,s), 2.48(3H,s),
7.36(2H,d,J=7.5Hz), 7.44(1H,dd,J=7.5, 4.5Hz), 7.92-8.03(4H,m),
8.07(1H,d,J=7.5Hz), 8.18(1H,d,J=7.5Hz), 8.95(1H,d,J=4.5Hz)

Preparation 42

Potassium (258.4 mg) was added to a suspension of the starting compound (1.5 g) in ethanol (40 ml), and the mixture was stirred at room temperature for 72 hours. The precipitate of potassium p-toluenesulfonate was removed by filtration, and the filtrate was diluted with diethyl ether (400 ml). A further precipitate of the potassium salt was filtered off, and the ethereal solution was extracted twice with 1.5N hydrochloric acid (50 ml). The combined extracts were evaporated in vacuo, and the residue was recrystallized from 2-propanol to give the object compound as an off-white solid (1.31 g).

mp : 293.5-296℃

MASS (ESI) (m/z) : 187 $(M+H)^+$

^{1}H-NMR (DMSO-d_6, δ) 4.72(1H,d,J=5.5Hz),
4.77(1H,d,J=5.5Hz), 7.83(1H,dd,J=7.5, 5.5Hz),
8.30(1H,d,J=7.5Hz), 8.37(1H,d,J=7.5Hz), 8.55(2H,br s),
8.81(1H,d,J=7.5Hz), 8.97(1H,s), 9.20(1H,d,J=5.5Hz)

Preparation 43

The object compound was obtained according to a similar manner to that of Preparation 28.

pale yellow solid

MASS (ESI) (m/z) : 434 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.42(9H,s), 3.15(2H,d,J=7.5Hz),
4.50(1H,m), 4.80(1H,dd,J=20.5, 5.5Hz),
4.89(1H,dd,J=20.5, 5.5Hz), 5.03(1H,m), 6.95(1H,m),
7.19-7.35(5H,m), 7.52(1H,dd,J=7.5, 5.5Hz), 8.16-8.27(2H,m),
8.30(1H,d,J=7.5Hz), 8.48(1H,s), 9.07(1H,d,J=5.5Hz)

Preparation 44

The object compound was obtained according to a similar manner to that of Preparation 2.

pale violet amorphous solid

MASS (ESI) (m/z) : 429 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.42(9H,s), 3.05(3H,s),
3.18(1H,dd,J=13.5, 8.5Hz), 3.37(1H,dd,J=13.5, 6.0Hz),
5.03(1H,m), 5.59(1H,br d,J=7.5Hz), 7.03-7.11(2H,m),
7.18(1H,s), 7.20-7.31(3H,m), 7.44(1H,dd,J=7.5, 5.5Hz),
7.57(1H,d,J=7.5Hz), 7.70(1H,s), 8.15(2H,t,J=7.5Hz),
8.95(1H,d,J=5.5Hz)

Preparation 45

The object compound was obtained according to a similar manner to that of Preparation 3.

pale yellow oil

MASS (ESI) (m/z) : 329 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.13-3.30(2H,m), 3.27(3H,s),
4.20(1H,t,J=7.5Hz), 7.08-7.15(2H,m), 7.18(1H,s),
7.21-7.34(3H,m) 7.43(1H,dd,J=7.5, 5.5Hz) 7.63(1H,d,J=7.5Hz),
7.73(1H,s), 8.15(2H,t,J=7.5Hz), 8.93(1H,d,J=5.5Hz)

Preparation 46

The object compound was obtained according to a similar manner to that of Preparation 40.

off-white solid

mp : 205-208℃

MASS (ESI) (m/z) : 187 $(M+H)^+$

^{1}H-NMR ($CDCl_3$-CD_3OD, δ) 2.40(3H,s), 7.59(1H,t,J=7.5Hz), 7.73(1H,t,J=7.5Hz), 7.87(1H,d,J=7.5Hz), 8.10(1H,d,J=7.5Hz), 8.28(1H,d,J=1.0Hz), 9.46(1H,d,J=1.0Hz)

Preparation 47

The object compound was obtained according to a similar manner to that of Preparation 41.

pale brown solid

mp : 165-174℃

MASS (ESI) (m/z) : 341 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 2.44(3H,s), 2.47(3H,s), 7.39(1H,d,J=7.5Hz), 7.60(1H,t,J=7.5Hz), 7.79(1H,t,J=7.5Hz), 7.85(1H,d,J=7.5Hz), 7.98(2H,d,J=7.5Hz), 8.11(1H,d,J=7.5Hz), 8.28(1H,d,J=1.5Hz), 9.14(1H,d,J=1.5Hz)

Preparation 48

The object compound was obtained according to a similar manner to that of Preparation 42.

off-white solid

mp : 290-294℃

MASS (ESI) (m/z) : 187 $(M+H)^+$

^{1}H-NMR (DMSO-d_6, δ) 4.75(1H,d,J=5.5Hz), 4.79(1H,d,J=5.5Hz), 7.80(1H,t,J=7.5Hz), 8.02(1H,t,J=7.5Hz), 8.18(1H,d,J=7.5Hz), 8.25(1H,d,J=7.5Hz), 8.61(2H,br s), 9.27(1H,d,J=1.0Hz), 9.41(1H,d,J=1.0Hz)

Preparation 49

The object compound was obtained according to a similar manner to that of Preparation 28.

pale yellow amorphous solid

MASS (ESI) (m/z) : 434 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.43(9H,s), 3.10-3.19(2H,m), 4.51(1H,m),

4.79(1H,dd,J=20.5, 4.5Hz), 4.88(1H,dd,J=20.5, 4.5Hz),
5.03(1H,m), 6.93(1H,m), 7.17-7.34(5H,m), 7.69(1H,t,J=7.5Hz),
7.90(1H,t,J=7.5Hz), 7.97(1H,d,J=7.5Hz), 8.18(1H,d,J=7.5Hz),
8.73(1H,d,J=1.0Hz), 9.40(1H,d,J=1.0Hz)

Preparation 50

The object compound was obtained according to a similar manner to that of Preparation 2.

pale brown amorphous solid

MASS (ESI) (m/z) : 429 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.45(9H,s), 3.03(3H,s),
3.17(1H,dd,J=13.0, 9.0Hz), 3.39(1H,dd,J=13.0, 5.5Hz),
5.05(1H,m), 5.63(1H,d,J=7.5Hz), 7.03-7.12(2H,m),
7.19-7.38(4H,m), 7.60(1H,t,J=7.5Hz), 7.76(1H,t,J=7.5Hz),
7.83(1H,d,J=7.5Hz), 8.00(1H,d,J=1.0Hz), 8.12(1H,d,J=7.5Hz),
8.80(1H,d,J=1.0Hz)

Preparation 51

The object compound was obtained according to a similar manner to that of Preparation 3.

pale brown amorphous solid

MASS (ESI) (m/z) : 329 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.18-3.25(2H,m), 3.22(3H,s),
4.21(1H,t,J=7.5Hz), 7.06-7.13(2H,m), 7.20-7.36(4H,m),
7.60(1H,t,J=7.5Hz), 7.76(1H,t,J=7.5Hz), 7.83(1H,d,J=7.5Hz),
8.04(1H,d,J=1.5Hz), 8.12(1H,d,J=7.5Hz), 8.83(1H,d,J=1.5Hz)

Preparation 52

The object compound was obtained according to a similar manner to that of Preparation 1.

mp : 144-146℃

MASS : 413 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.41(9H,s), 3.00-3.20(2H,m),
3.87(3H,s), 4.49(1H,d,J=5Hz), 4.53-4.74(2H,m),
5.08(1H,d,J=5Hz), 6.95(3H,d,J=8Hz), 7.19-7.32(5H,m),

7.92(2H,d,J=8Hz)

Preparation 53

The object compound was obtained according to a similar manner to that of Preparation 2.

mp : 125-128℃

MASS : 408 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.38(9H,s), 2.93(3H,s),
3.11(1×1/3H,d,J=8Hz), 3.17(1×2/3H,d,J=8Hz),
3.31(1×2/3H,d,J=6Hz), 3.37(1×1/3H,d,J=6Hz),
3.83(3H,s), 4.99(1H,q,J=8Hz), 5.59(1H,d,J=8Hz),
6.92(2H,d,J=8Hz), 6.98(1H,s), 7.00-7.10(2H,m)
7.14(2H,d,J=8Hz), 7.20-7.30(3H,m)

Preparation 54

The object compound was obtained according to a similar manner to that of Preparation 3.

oil

MASS : 308 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 3.08-3.28(2H,m), 3.12(3H,s),
3.81(3H,s), 4.17(1H,t,J=8Hz), 6.94(2H,d,J=8Hz),
6.99(1H,s), 7.09(2H,d,J=8Hz), 7.11-7.40(5H,m)

Preparation 55

The object compound was obtained according to a similar manner to that of Preparation 32.

colorless solid

mp : 144-150℃

MASS (ESI) (m/z) : 408 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.37(9H,s), 3.20(2H,m), 3.78(3H,s),
4.59(1H,d,J=14.5Hz), 4.70(1H,d,J=14.5Hz), 5.03(1H,m),
5.35(1H,m), 6.61(1H,s), 6.76(2H,d,J=9.0Hz),
6.81(2H,d,J=9.0Hz), 6.97-7.06(3H,m), 7.17-7.23(3H,m)

Preparation 56

The object compound was obtained according to a similar manner to

that of Preparation 3.

off-white oil

MASS (ESI) (m/z) : 308 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.03(1H,dd,J=14.5, 7.5Hz),
3.14(1H,dd,J=14.5, 7.5Hz), 3.77(3H,s), 4.09(1H,t,J=7.5Hz),
4.73(1H,d,J=15.0Hz), 4.81(1H,d,J=15.0Hz), 6.71(1H,s),
6.81(2H,d,J=7.5Hz), 6.91(2H,d,J=7.5Hz), 7.01-7.07(3H,s),
7.19-7.30(3H,m)

Preparation 57

The object compound was obtained according to a similar manner to that of Preparation 28.

pale yellow oil

MASS (ESI) (m/z) : 367 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.47(9H,s), 1.98(1H,m), 2.13(3H,s),
2.16(1H,m), 2.61(2H,t,J=7.5Hz), 4.41(1H,m),
4.77(2H,t,J=4.5Hz), 5.23(1H,m), 7.14(1H,m),
7.50(2H,t,J=7.5Hz), 7.63(1H,t,J=7.5Hz), 7.98(2H,d,J=7.5Hz)

Preparation 58

The object compound was obtained according to a similar manner to that of Preparation 2.

pale brown oil

MASS (ESI) (m/z) : 362 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.43(9H,s), 2.12(3H,s), 2.12-2.61(4H,m),
3.63(3H,s), 5.05-5.26(2H,m), 7.01(1H,s), 7.33-7.51(5H,m)

Preparation 59

The object compound was obtained according to a similar manner to that of Preparation 3.

pale yellow oil

MASS (ESI) (m/z) : 262 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 2.08(1H,m), 2.11(3H,s), 2.25(1H,m),
2.55-2.77(2H,m), 3.61(3H,s), 4.20(1H,t,J=7.5Hz), 7.01(1H,s),
7.33-7.48(5H,m)

Preparation 60

To a solution of the starting compound (893 mg) in tetrahydrofuran (4.5 ml) was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (552 mg). The mixture was stirred at 50℃ for 4.5 hours, then allowed to cool to room temperature and concentrated. The crude product was purified by column chromatography (silica gel, chloroform) to give the object compound as pale orange powder (476 mg).

MASS (ESI) (m/z) : 489, 491 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, 300MHz) δ : 1.41(9H,s), 3.12-3.32(2H,m), 3.76(3H,s), 5.11-5.31(2H,m), 6.80(2H,d,J=8Hz), 7.02(2H,d,J=8Hz), 7.36(2H,d,J=8Hz), 7.50(2H,d,J=8Hz), 7.87(1H,s)

Preparation 61

The object compound was obtained according to a similar manner to that of Preparation 9.

MASS (ESI) (m/z) : 389,391 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, 300MHz) δ : 2.84(1H,dd,J=13 and 9Hz), 3.31(1H,dd,J=13 and 5Hz), 3.78(3H,s), 4.46(1H,dd,J=9 and 5Hz), 6.86(2H,d,J=8Hz), 7.13(2H,d,J=8Hz), 7.40(2H,d,J=8Hz), 7.51(2H,d,J=8Hz), 7.88(1H,s)

Preparation 62

The object compound was obtained according to a similar manner to that of Preparation 28.

mp : 140-143℃

MASS : 427 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.38(9H,s), 1.43(3H,t,J=8Hz), 3.00-3.19(2H,m), 4.11(2H,q,J=8Hz), 4.40-4.72(3H,m), 4.96-5.10(1H,m), 6.90(1H,br s), 6.92(2H,d,J=8Hz), 7.13-7.35(5H,m), 7.91(2H,d,J=8Hz)

Preparation 63

The object compound was obtained according to a similar manner to

that of Preparation 2.

mp : 86-91℃

MASS : 422 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.41(9H,s), 1.42(3H,t,J=8Hz), 2.92(3H,s), 3.11(1×1/3H,d,J=10Hz), 3.18(1×2/3H,d,J=10Hz), 3.31(1×2/3H,d,J=6Hz), 3.36(1×1/3H,d,J=6Hz), 4.05(2H,q,J=8Hz), 5.00(1H,q,J=8Hz), 5.60(1H,d,J=8Hz), 6.91(2H,d,J=8Hz), 6.99(1H,s), 7.00-7.09(2H,m), 7.13(2H,d,J=8Hz), 7.19-7.25(3H,m)

Preparation 64

The object compound was obtained according to a similar manner to that of Preparation 3 except that a mixutre of trifluoroacetic acid and dichloromethane was used instead of trifluoroacetic acid.

MASS : 322 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.43(3H,t,J=8Hz), 3.09-3.27(2H,m), 3.12(3H,s), 4.07(2H,q,J=8Hz), 4.13(1H,t,J=8Hz), 6.91(2H,d,J=8Hz), 7.00(1H,s), 7.10(2H,d,J=7Hz), 7.19(2H,d,J=8Hz), 7.21-7.31(3H,m)

Preparation 65

The object compound was obtained according to a similar manner to that of Preparation 28.

amorphous solid

MASS : 411 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.29(3H,t,J=8Hz), 1.40(9H,s), 2.71(2H,q,J=8Hz), 3.00-3.20(2H,m), 4.40-4.53(1H,m), 4.58-4.80(2H,m), 5.00-5.15(1H,m), 6.94(1H,s), 7.12-7.40(7H,m), 7.88(2H,d,J=8Hz)

Preparation 66

The object compound was obtained according to a similar manner to that of Preparation 2.

oil

MASS : 406 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.22(3H,t,J=8Hz), 1.40(9H,s), 2.67(2H,q,J=8Hz), 2.93(3H,s), 3.08-3.20(1H,m), 3.30-3.40(1H,m), 5.00(1H,q,J=8Hz), 5.69(1H,d,J=8Hz), 7.00(1H,s), 7.01-7.10(2H,m), 7.10-7.18(2H,m), 7.18-7.32(5H,m)

Preparation 67

The object compound was obtained according to a similar manner to that of Preparation 64.

oil

MASS : 306 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.30(3H,t,J=8Hz), 2.68(2H,q,J=8Hz), 3.09-3.28(2H,m), 3.18(3H,s), 4.13(1H,t,J=8Hz), 7.01(1H,s), 7.04-7.10(2H,m), 7.12-7.30(7H,m)

Preparation 68

The object compound was obtained according to a similar manner to that of Preparation 28.

oil

MASS : 447 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.40(9H,s), 3.02(2H,d,J=6Hz), 3.76(3H,s), 4.33-4.47(1H,m), 4.50-4.71(2H,m), 4.91-5.30(1H,m), 6.72-6.80(1H,m), 6.81(2H,d,J=8Hz), 7.11(2H,d,J=8Hz), 7.30-7.40(1H,m), 7.41-7.48(2H,m), 7.51(1H,d,J=8Hz)

Preparation 69

The object compound was obtained according to a similar manner to that of Preparation 2.

oil

MASS : 442 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.47(9H,s), 2.86(3H,s), 3.01-3.12(1H,m), 3.22-3.31(1H,m), 3.73(3H,s), 4.89-5.00(1H,m), 5.61(1H,d,J=8Hz), 6.73(2H,d,J=8Hz), 6.97(2H,d,J=8Hz), 7.00(1H,s), 7.20-7.39(3H,m), 7.44(1H,d,J=8Hz)

Preparation 70

The object compound was obtained according to a similar manner to

that of Preparation 64.

oil

MASS : 342 (M+1)

^{1}H-NMR ($CDCl_3$) δ 3.04(3H,s), 3.08-3.17(2H,m), 3.75(3H,s), 4.11(1H,t,J=8Hz), 6.80(2H,d,J=8Hz), 7.00(2H,d,J=8Hz), 7.01(1H,s), 7.21-7.40(3H,m), 7.47(1H,d,J=7Hz)

Preparation 71

The object compound was obtained according to a similar manner to that of Preparation 28.

mp : 115-122℃

MASS : 427 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.42(9H,s), 2.42(3H,s), 3.07(2H,d,J=7Hz), 3.76(3H,s), 4.38-4.50(1H,m), 4.58-4.77(2H,m), 4.98-5.10(1H,m), 6.81(2H,d,J=8Hz), 6.87-6.92(1H,m), 7.11(2H,d,J=8Hz), 7.29(2H,d,J=8Hz), 7.85(2H,d,J=8Hz)

Preparation 72

The object compound was obtained according to a similar manner to that of Preparation 2.

oil

MASS : 422 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.42(9H,s), 2.38(3H,s), 2.99(3H,s), 3.01-3.18(1H,m), 3.20-3.30(1H,m), 3.71(3H,s), 4.93(1H,q,J=8Hz), 5.58(1H,d,J=8Hz), 6.73(2H,d,J=8Hz), 6.93(2H,d,J=8Hz), 7.00(1H,s), 7.11(2H,d,J=7Hz), 7.20(2H,d,J=7Hz)

Preparation 73

The object compound was obtained according to a similar manner to that of Preparation 64.

oil

MASS : 322 (M+1)

^{1}H-NMR ($CDCl_3$) δ 2.39(3H,s), 3.10(1H,t,J=8Hz), 3.19(3H,s), 3.80(3H,s), 4.12(1H,t,J=8Hz), 6.81(2H,d,J=8Hz),

7.00(2H,d,J=8Hz), 7.01(1H,s), 7.12-7.23(5H,m)

Preparation 74

The object compound was obtained according to a similar manner to that of Preparation 28.

mp : 105-108℃

MASS : 447 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.40(9H,s), 3.06(2H,d,J=7Hz), 3.79(3H,s), 4.41(1H,br s), 4.58-4.77(2H,m), 4.99(1H,br s), 6.81(2H,d,J=8Hz), 6.83(1H,s), 7.12(2H,d,J=8Hz), 7.49(2H,d,J=7Hz), 7.90(2H,d,J=7Hz)

Preparation 75

The object compound was obtained according to a similar manner to that of Preparation 2.

amorphous solid

^{1}H-NMR ($CDCl_3$) δ 1.40(9H,s), 2.98-3.13(1H,m), 3.00(3H,s), 3.21-3.32(1H,m), 3.78(3H,s), 4.90-5.02(1H,m), 5.57(1H,d,J=8Hz), 6.78(2H,d,J=8Hz), 6.93(2H,d,J=8Hz), 7.02(1H,s), 7.18(2H,d,J=8Hz), 7.38(2H,d,J=8Hz)

Preparation 76

The object compound was obtained according to a similar manner to that of Preparation 64.

oil

^{1}H-NMR ($CDCl_3$) δ 3.11(2H,t,J=7Hz), 3.19(3H,s), 3.80(3H,s), 4.11(1H,t,J=8Hz), 6.80(2H,d,J=8Hz), 7.00(2H,d,J=8Hz), 7.02(1H,s), 7.20(2H,d,J=8Hz), 7.38(2H,d,J=8Hz)

Preparation 77

The object compound was obtained according to a similar manner to that of Preparation 28.

amorphous solid

MASS : 447 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.40(9H,s), 3.07(2H,d,J=6Hz), 3.73(3H,s), 4.42(1H,br s), 4.58-4.80(2H,m), 5.01(1H,br s),

6.81(2H,d,J=8Hz), 6.84(1H,br s), 7.11(2H,d,J=8Hz),
7.42(1H,t,J=8Hz), 7.59(1H,d,J=8Hz), 7.81(1H,d,J=8Hz),
7.91(1H,s)

Preparation 78

The object compound was obtained according to a similar manner to that of Preparation 2.

amorphous solid

MASS : 442 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.43(9H,s), 3.00(3H,s), 3.11-3.32(2H,m),
3.79(3H,s), 4.91-5.03(1H,m), 5.88(1H,br s), 6.78(2H,d,J=8Hz),
6.93(2H,d,J=8Hz), 7.03-7.19(2H,m), 7.21(1H,s),
7.30-7.40(2H,m)

Preparation 79

The object compound was obtained according to a similar manner to that of Preparation 64.

oil

MASS : 342 (M+1)

^{1}H-NMR ($CDCl_3$) δ 3.07-3.20(2H,m), 3.18(3H,s), 3.78(3H,s),
4.20(1H,t,J=8Hz), 6.80(2H,d,J=8Hz), 6.99(2H,d,J=8Hz),
7.09(1H,s), 7.11-7.21(1H,m), 7.28(1H,s), 7.30-7.40(2H,m)

Preparation 80

The object compound was obtained according to a similar manner to that of Preparation 28.

mp : 120-123℃

MASS : 431 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.43(9H,s), 3.08(2H,d,J=8Hz), 3.76(3H,s),
4.42(1H,br s), 4.58-4.78(2H,m), 5.00(1H,br s),
6.82(2H,d,J=8Hz), 6.87(1H,s), 7.10-7.22(4H,m),
8.00(2H,t,J=7Hz)

Preparation 81

The object compound was obtained according to a similar manner to that of Preparation 2.

amorphous solid

MASS : 426 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.41(9H,s), 2.99(3H,s), 3.01-3.32(2H,m), 3.74(3H,s), 4.90-5.02(1H,m), 5.70(1H,d,J=7Hz), 6.76(2H,d,J=8Hz), 6.95(2H,d,J=8Hz), 7.01(1H,s), 7.03-7.16(2H,m), 7.16-7.23(2H,m)

Preparation 82

The object compound was obtained according to a similar manner to that of Preparation 64.

oil

MASS : 326 (M+1)

^{1}H-NMR ($CDCl_3$) δ 3.08-3.22(2H,m), 3.18(3H,s), 3.80(3H,s), 4.18(1H,t,J=8Hz), 6.80(2H,d,J=8Hz), 6.99(2H,d,J=8Hz), 7.00(1H,s), 7.09(2H,t,J=8Hz), 7.20-7.30(2H,m)

Preparation 83

The object compound was obtained according to a similar manner to that of Preparation 28.

mp : 131-134℃

MASS : 457 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.43(9H,s), 1.47(3H,t,J=8Hz), 3.05(2H,d,J=8Hz), 3.77(3H,s), 4.10(2H,q,J=8Hz), 4.41(1H,br s), 4.51-4.73(2H,m), 5.01(1H,br s), 6.80(2H,d,J=8Hz), 6.90(1H,br s), 6.92(2H,d,J=8Hz), 7.11(2H,d,J=8Hz), 7.91(2H,d,J=8Hz)

Preparation 84

The object compound was obtained according to a similar manner to that of Preparation 2.

solid

MASS : 452 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.41(9H,s), 1.44(3H,t,J=8Hz), 2.99(3H,s), 3.01-3.13(1H,m), 3.20-3.31(1H,m), 3.78(3H,s), 4.03(2H,q,J=8Hz), 4.88-4.98(1H,m), 5.58(1H,q,J=8Hz), 6.78(2H,d,J=8Hz), 6.88-7.00(5H,m), 7.12(2H,d,J=8Hz)

Preparation 85

The object compound was obtained according to a similar manner to that of Preparation 64.

oil

MASS : 352 (M+1)

^{1}H-NMR ($CDCl_3$) δ 1.43(3H,t,J=8Hz), 3.02-3.17(2H,m), 3.18(3H,s), 3.75(3H,s), 4.00-4.18(1H,m), 4.05(2H,q,J=8Hz), 6.80(2H,d,J=8Hz), 6.91(2H,d,J=8Hz), 6.98(1H,s), 7.00(2H,d,J=8Hz), 7.19(2H,d,J=8Hz)

Preparation 86

A solution of potassium tert-butoxide (4.2 g) in anhydrous tetrahydrofuran (70 ml) was cooled under nitrogen atmosphere to -70°C, and a solution of the starting compound (10 g) in anhydrous tetrahydrofuran (35 ml) was added while maintaining the reaction temperature at -70°C. After 30 minutes, this solution was added dropwise to a solution of 4-bromobenzoyl chloride (8.21 g) in anhydrous tetrahydrofuran (24 ml) with stirring while cooling at -70°C on a cooling bath. The reaction mixture was stirred at -70°C for 1 hour and quenched with 3N-hydrochloric acid (100 ml). The cooling bath was removed and the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in water (15 ml) and extracted with diethyl ether (twice). The aqueous layer was concentrated *in vacuo*, and the residue was dissolved in anhydrous methanol. The precipitated white solid (KCl) was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was crystallized from tetrahydrofuran/diethyl ether to give the object compound as an off-white solid.

mp : 183-188°C

MASS : 286 $(M+H)^+$

^{1}H-NMR (DMSO-d_6, δ) 1.03(3H,t,J=7.0Hz), 4.13(2H,q,J=7.0Hz), 6.24(1H,s), 7.86(2H,d,J=7.5Hz), 8.09(2H,d,J=7.5Hz), 9.10(2H,br s),

Preparation 87

The object compound was obtained according to a similar manner to that of Preparation 28.

pale yellow amorphous solid

MASS : 531 $(M-H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.14(3H,t,J=7.0Hz), 1.40(9H,s), 2.97-3.18(2H,m), 4.16(2H,q,J=7.0Hz), 4.49(1H,m), 4.96(1H,m), 6.03(1H×3/7,d,J=7.0Hz), 6.06(1H×4/7,d,J=7.0Hz), 7.14-7.31(6H,m), 7.64(2H,d,J=7.5Hz), 7.95(2H×3/7,d,J=7.5Hz), 7.97(2H×4/7,d,J=7.5Hz)

Preparation 88

The object compound was obtained according to a similar manner to that of Preparation 2.

pale yellow amorphous solid

MASS : 528 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.18(3H,t,J=7.0Hz), 1.41(9H,s), 2.69(3H,s), 3.17(1H,dd,J=13.5 and 9.0Hz), 3.37(1H,dd,J=13.5 and 7.0Hz), 4.23(2H,q,J=7.0Hz), 4.98(1H,m), 5.74(1H,d,J=7.5Hz), 6.97-7.08(4H,m), 7.19-7.27(3H,m), 7.55(2H,d,J=7.5Hz)

Preparation 89

The object compound was obtained according to a similar manner to that of Preparation 3.

pale yellow oil

MASS : 428 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.20(3H,t,J=7.0Hz), 2.97(3H,s), 3.22(2H,d,J=7.0Hz), 4.19(1H,t,J=7.0Hz), 4.25(2H,q,J=7.0Hz), 7.05-7.15(4H,m), 7.21-7.33(3H,m), 7.57(2H,d,J=7.5Hz)

Preparation 90

The object compound was obtained according to a similar manner to that of Preparation 28.

pale yellow solid

mp : 148-152.5℃

MASS : 383 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.41(9H,s), 3.12(2H,d,J=7.0Hz), 4.49(1H,m), 4.65(1H,dd,J=20.5 and 5.5Hz), 4.75(1H,dd,J=20.5 and 5.5Hz), 5.03(1H,m), 6.89(1H,m), 7.28-7.32(5H,m), 7.50(2H,t,J=7.5Hz), 7.62(1H,t,J=7.5Hz), 7.94(2H,d,J=7.5Hz)

Preparation 91

The object compound was obtained according to a similar manner to that of Preparation 2.

brown amorphous solid

MASS : 378 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 1.42(9H,s), 2.97(3H,s), 3.14(1H,dd,J=13.5 and 9.0Hz), 3.35(1H,dd,J=13.5 and 7.0Hz), 5.01(1H,m), 5.59(1H,d,J=7.5Hz), 7.01-7.08(2H,m), 7.03(1H,s), 7.17-7.29(5H,m), 7.32-7.44(3H,m)

Preparation 92

The object compound was obtained according to a similar manner to that of Preparation 3.

brown oil

MASS : 278 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.14(1H,dd,J=13.5 and 7.5Hz), 3.18(3H,s), 3.21(1H,dd,J=13.5 and 7.5Hz), 4.15(1H,t,J=7.5Hz), 7.05(1H,s), 7.09(2H,d,J=7.5Hz), 7.19-7.44(8H,m)

Preparation 93

The object compound was obtained according to a similar manner to that of Preparation 28.

MASS (ESI) (m/z) : 503, 505 $(M-H)^-$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.38(3H,t,J=7Hz), 1.41(9H,s), 3.04(2H,d,J=7Hz), 3.98(2H,q,J=7Hz), 4.32-4.49(1H,m), 4.53-4.77(2H,m), 4.99(1H,br d,J=8Hz), 6.80(2H,d,J=8Hz), 6.83(1H,br s), 7.10(2H,d,J=8Hz), 7.62(2H,d,J=8Hz), 7.80(2H,d,J=8Hz)

Preparation 94

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 500, 502 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.39(3H,t,J=7Hz), 1.41(9H,s), 2.99(3H,s), 3.05(1H,dd,J=13 and 9Hz), 3.25(1H,dd,J=13 and 5Hz), 3.98(2H,q,J=7Hz), 4.86-5.02(1H,m), 5.56(1H,br d,J=8Hz), 6.73(2H,d,J=8Hz), 6.91(2H,d,J=8Hz), 7.01(1H,s), 7.09(2H,d,J=8Hz), 7.51(2H,d,J=8Hz)

Preparation 95

The object compound was obtained according to a similar manner to that of Preparation 9.

MASS (ESI) (m/z) : 400, 402 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.40(3H,t,J=7Hz), 3.00-3.18(2H,m), 3.19(3H,s), 4.00(2H,q,J=7Hz), 4.10(1H,t,J=7Hz), 6.80(2H,d,J=8Hz), 6.96(2H,d,J=8Hz), 7.04(1H,s), 7.15(2H,d,J=8Hz), 7.54(2H,d,J=8Hz)

Preparation 96

The object compound was obtained according to a similar manner to that of Preparation 28.

MASS (ESI) (m/z) : 491, 493 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.41(9H,s), 2.92-3.18(2H,m), 3.87(3H,s), 4.40-4.53(1H,m), 4.53-4.78(2H,m), 5.02(1H,br d,J=8Hz), 6.95(2H,d,J=8Hz), 6.98(1H,br s), 7.09(2H,d,J=8Hz), 7.40(2H,d,J=8Hz), 7.93(2H,d,J=8Hz)

Preparation 97

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 486, 488 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.40(9H,s), 3.09(3H,s), 3.10-3.31(2H,m), 3.83(3H,s), 4.91-5.06(1H,m), 5.48(1H,br d,J=8Hz), 6.88-7.01(5H,m), 7.17(2H,d,J=8Hz), 7.35(2H,d,J=8Hz)

Preparation 98

The object compound was obtained according to a similar manner to that of Preparation 9.

MASS (ESI) (m/z) : 386, 388 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 3.02-3.25(2H,m), 3.23(3H,s), 3.83(3H,s), 4.12(1H,t,J=7Hz), 6.89-7.02(5H,m), 7.20(2H,d,J=8Hz), 7.38(2H,d,J=8Hz)

Preparation 99

The object compound was obtained according to a similar manner to that of Preparation 28.

MASS (ESI) (m/z) : 455 $(M-H)^-$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.39(3H,t,J=7Hz), 1.42(9H,s), 2.96-3.12(2H,m), 3.88(3H,s), 3.98(2H,q,J=7Hz), 4.33-4.51(1H,m), 4.52-4.79(2H,m), 4.93-5.11(1H,m), 6.81(2H,d,J=8Hz), 6.92(1H,br s), 6.95(2H,d,J=8Hz), 7.10(2H,d,J=8Hz), 7.92(2H,d,J=8Hz)

Preparation 100

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 452 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.39(3H,t,J=7Hz), 1.41(9H,s), 2.97(3H,s), 3.00-3.31(2H,m), 3.81(3H,s), 3.98(2H,q,J=7Hz), 4.86-5.01(1H,m), 5.62(1H,br d,J=8Hz), 6.74(2H,d,J=8Hz), 6.85-6.95(4H,m), 6.96(1H,s), 7.15(2H,d,J=8Hz)

Preparation 101

The object compound was obtained according to a similar manner to that of Preparation 9.

MASS (ESI) (m/z) : 352 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.40(3H,t,J=7Hz), 3.00-3.19(2H,m), 3.17(3H,s), 3.82(3H,s), 4.00(2H,q,J=7Hz), 4.10(1H,t,J=7Hz), 6.80(2H,d,J=8Hz), 6.89-7.02(5H,m), 7.20(2H,d,J=8Hz)

Preparation 102

The object compound was obtained according to a similar manner to

that of Preparation 28.

MASS (ESI) (m/z) : 441 $(M-H)^-$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.42(9H,s), 3.06(2H,d,J=7Hz), 3.76(3H,s), 3.88(3H,s), 4.34-4.52(1H,m), 4.54-4.79(2H,m), 4.91-5.10(1H,m), 6.82(2H,d,J=8Hz), 6.91(1H,br s), 6.96(2H,d,J=8Hz), 7.12(2H,d,J=8Hz), 7.93(2H,d,J=8Hz)

Preparation 103

The object compound was obtained according to a similar manner to that of Preparation 2.

MASS (ESI) (m/z) : 438 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 1.41(9H,s), 2.98(3H,s), 3.01-3.31(2H,m), 3.76(3H,s), 3.81(3H,s), 4.88-5.00(1H,m), 5.59(1H,br d,J=8Hz), 6.77(2H,d,J=8Hz), 6.87-7.00(5H,m), 7.14(2H,d,J=8Hz)

Preparation 104

The object compound was obtained according to a similar manner to that of Preparation 9.

MASS (ESI) (m/z) : 338 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ 3.01-3.20(2H,m), 3.18(3H,s), 3.78(3H,s), 3.83(3H,s), 4.10(1H,t,J=7Hz), 6.81(2H,d,J=8Hz), 6.89-7.05(5H,m), 7.20(2H,d,J=8Hz)

Example 1

To an ice-cooled solution of the starting compound (76 mg), indole-2-carboxylic acid (66 mg) and 1-hydroxybenzotriazole (58 mg) in dichloromethane (1 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg). The mixture was stirred at room temperature for 12 hours. A saturated aqueous sodium hydrogencarbonate solution was added to the mixture, and then the mixture was extracted three times with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica gel, chloroform/methanol=70/1) to give the object compound as

white powder (128 mg).

MASS (ESI) (m/z) : 331 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.62(3H,s), 4.80(2H,d,J=5Hz), 6.98-7.92(12H,m), 9.50(1H,br s)

Example 2

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 332 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.64(3H,s), 4.80(2H,d,J=5Hz), 7.05(1H,s), 7.20-7.72(12H,m)

Example 3

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 493 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.06(3H,t,J=7Hz), 2.81(3H,s), 3.42-3.65(2H,m), 4.17(2H,q,J=7Hz), 5.48-5.64(1H,m), 6.88-7.63(15H,m), 8.41(1H,br s), 9.50(1H,br s)

Example 4

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 494 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.12(3H,t,J=7Hz), 2.81(3H,s), 3.32-3.56(2H,m), 4.22(2H,q,J=7Hz), 5.48-5.62(1H,m), 7.05-7.70(15H,m), 7.82(1H,br d,J=8Hz)

Example 5

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 451 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.09(3H,s), 3.22-3.50(2H,m), 3.72(3H,s), 5.50-5.64(1H,m), 6.72(2H,d,J=8Hz), 6.96(2H,d,J=8Hz), 7.00-7.65(11H,m), 8.13(1H,br d,J=8Hz), 10.50(1H,br s)

Example 6

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 452 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.06(3H,s), 3.17-3.48(2H,m), 3.75(3H,s), 5.41-5.56(1H,m), 6.77(2H,d,J=8Hz), 6.98(2H,d,J=8Hz), 7.10(1H,s), 7.18-7.80(11H,m)

Example 7

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 529, 531 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.08(3H,s), 3.22-3.50(2H,m), 3.72(3H,s), 5.50-5.64(1H,m), 6.72(2H,d,J=8Hz), 6.98(2H,d,J=8Hz), 7.00-7.65(10H,m), 8.11(1H,br d,J=8Hz), 9.95(1H,br s)

Example 8

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 530, 532 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.06(3H,s), 3.15-3.48(2H,m), 3.75(3H,s), 5.40-5.55(1H,m), 6.77(2H,d,J=8Hz), 6.98(2H,d,J=8Hz), 7.05-7.75(11H,m)

Example 9

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 467 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 2.50(3H,s), 3.01(3H,s), 3.22-3.56(2H,m), 5.51-5.66(1H,m), 6.98-7.68(15H,m), 7.95(1H,br d,J=8Hz), 9.60(1H,br s)

Example 10

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 468 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 2.50(3H,s), 3.00(3H,s),
3.22-3.55(2H,m), 5.46-5.60(1H,m), 7.02-7.80(16H,m)

Example 11

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 533, 535 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.18(3H,s), 3.30-3.48(2H,m),
5.52-5.68(1H,m), 6.93-8.00(15H,m), 9.78(1H,br s)

Example 12

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 534, 536 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.18(3H,s), 3.26-3.49(2H,m),
5.47-5.61(1H,m), 6.98-7.70(15H,m)

Example 13

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS (ESI) (m/z) : 499 $(M+H)^+$

^{1}H-NMR ($CDCl_3$+CD_3OD,300MHz) δ : 2.88(3H,s),
3.00(1×1/3H,d,J=8Hz), 3.03(1×2/3H,d,J=8Hz),
3.11(1×2/3H,d,J=4Hz), 3.16(1×1/3H,d,J=4Hz),
5.30(1H,q,J=6Hz), 6.70-6.90(6H,m), 6.90-7.04(5H,m),
7.10(1H,s), 7.16(1H,d,J=8Hz), 7.26(2H,d,J=8Hz),
7.40(1H,d,J=8Hz)

Example 14

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS (ESI) (m/z) : 500 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 2.99(3H,s),

3.30(1×1/3H,d,J=8Hz), 3.32(1×2/3H,d,J=8Hz),
3.49(1×2/3H,d,J=4Hz), 3.51(1×1/3H,d,J=4Hz),
5.49-5.60(1H,m), 7.00-7.19(5H,m), 7.19-7.32(4H,m),
7.40(1H,t,J=8Hz), 7.49(1H,s), 7.52(3H,d,J=8Hz),
7.64(1H,d,J=8Hz), 7.93(1H,d,J=8Hz)

Example 15

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid
MASS (ESI) (m/z) : 455 $(M+H)^+$
^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.01(3H,s),
3.32(1×1/3H,d,J=8Hz), 3.39(1×2/3H,d,J=8Hz),
3.49(1×2/3H,d,J=4Hz), 3.52(1×1/3H,d,J=4Hz),
5.60(1H,q,J=8Hz), 7.00-7.19(7H,m), 7.19-7.30(4H,m),
7.30-7.43(3H,m), 7.61(1H,d,J=8Hz), 8.17(1H,d,J=8Hz),
9.88(1H,s)

Example 16

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid
MASS (ESI) (m/z) : 456 $(M+H)^+$
^{1}H-NMR ($CDCl_3$,300MHz) δ : 2.99(3H,s),
3.29(1×1/3H,d,J=8Hz), 3.32(1×2/3H,d,J=8Hz),
3.49(1×2/3H,d,J=4Hz), 3.52(1×1/3H,d,J=4Hz),
5.48-5.60(1H,m), 7.03-7.11(3H,m), 7.15(2H,d,J=8Hz),
7.20-7.31(4H,m), 7.38(2H,d,J=8Hz), 7.41-7.58(3H,m),
7.67(1H,d,J=8Hz), 7.80(1H,d,J=8Hz)

Example 17

The object compound was obtained according to a similar manner to that of Example 1.

mp : 145-150℃
MASS (ESI) (m/z) : 435 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 2.31(3H,s), 3.02(3H,s),
3.33-3.57(2H,m), 5.60-5.73(1H,m), 7.00-7.12(7H,m),
7.12-7.22(6H,m), 7.36(1H,d,J=8Hz), 7.59(1H,d,J=8Hz),
8.57(1H,d,J=8Hz)

Example 18

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS (ESI) (m/z) : 436 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 2.38(3H,s), 3.00(3H,s),
3.30(1×1/3H,d,J=8Hz), 3.38(1×2/3H,d,J=8Hz),
3.50(1×2/3H,d,J=4Hz), 3.52(1×1/3H,d,J=4Hz),
5.48-5.62(1H,m), 7.02-7.14(5H,m), 7.16-7.33(6H,m),
7.35-7.55(3H,m), 7.65(1H,d,J=8Hz), 7.91(1H,d,J=8Hz)

Example 19

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS (ESI) (m/z) : 455 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.18(3H,s), 3.40-3.50(2H,m),
5.70(1H,q,J=8Hz), 6.98-7.29(10H,m), 7.30-7.42(4H,m),
7.59(1H,d,J=8Hz), 8.60(1H,d,J=8Hz)

Example 20

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS (ESI) (m/z) : 456 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.19(3H,s), 3.30-3.51(2H,m),
5.49-5.60(1H,m), 7.04(2H,d,J=8Hz), 7.10(1H,s),
7.14-7.31(5H,m), 7.31-7.52(6H,m), 7.64(1H,d,J=8Hz),
7.78(1H,d,J=8Hz)

Example 21

The object compound was obtained according to a similar manner to that of Example 1.

colorless solid

mp : 223-226℃

MASS (ESI) (m/z) : 435 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, 300MHz) δ : 2.23(3H,s), 3.23-3.40(2H,m), 4.77(1H,d,J=16.0Hz), 4.83(1H,d,J=16.0Hz), 5.60(1H,q,J=7.5Hz), 6.70(1H,s), 6.78(2H,d,J=7.5Hz), 6.93(1H,s), 6.97-7.29(10H,m), 7.37(1H,d,J=7.5Hz), 7.58(1H,d,J=7.5Hz), 7.62(1H,d,J=7.5Hz), 9.47(1H,br s)

Example 22

The object compound was obtained according to a similar manner to that of Example 1.

pale yellow amorphous solid

MASS (ESI) (m/z) : 421 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.00(3H,s), 3.30(1H,dd,J=12.0, 8.5Hz), 3.49(1H,dd,J=12.0, 5.5Hz), 5.57(1H,m), 6.99-7.43(15H,m), 7.63(1H,d,J=7.5Hz), 7.76(1H,d,J=7.5Hz), 9.41(1H,s)

Example 23

The object compound was obtained according to a similar manner to that of Example 1.

colorless solid

mp : 234-239℃

MASS (ESI) (m/z) : 345 $(M+H)^+$

^{1}H-NMR ($CDCl_3$-CD_3OD, δ) 3.17(3H,s), 3.20(1H,dd,J=13.5, 9.0Hz), 3.34(1H,dd,J=13.5, 5.5Hz), 5.49(1H,dd,J=9.0, 5.5Hz), 6.66(1H,s), 6.97-7.03(3H,m), 7.13(1H,t,J=7.5Hz), 7.18-7.31(5H,m), 7.41(1H,d,J=7.5Hz), 7.68(1H,d,J=7.5Hz)

Example 24

The object compound was obtained according to a similar manner to that of Example 1.

colorless solid

mp : 251-256℃

MASS (ESI) (m/z) : 331 $(M+H)^+$

^{1}H-NMR ($CDCl_3$-CD_3OD, δ) 3.31(2H,d,J=7.5Hz), 5.39(1H,t,J=7.5Hz), 6.90(2H,s), 7.02-7.31(8H,m), 7.39(1H,d,J=7.5Hz), 7.64(1H,d,J=7.5Hz)

Example 25

The object compound was obtained according to a similar manner to that of Example 1.

off-white solid

mp : 202-206℃

MASS (ESI) (m/z) : 472 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.10(3H,s), 3.35(1H,dd,J=13.5, 8.5Hz), 3.53(1H,dd,J=13.5, 5.5Hz), 5.61(1H,m), 7.03(1H,s), 7.09-7.17(3H,m), 7.20(1H,s), 7.23-7.32(4H,m), 7.38-7.46(2H,m), 7.56(1H,dd,J=7.5, 2.5Hz), 7.65(1H,d,J=7.5Hz), 7.67(1H,s), 7.75(1H,d,J=7.5Hz), 8.11(2H,d,J=7.5Hz), 8.93(1H,d,J=5.5Hz), 9.40(1H,s)

Example 26

The object compound was obtained according to a similar manner to that of Example 1.

off-white amorphous solid

MASS (ESI) (m/z) : 472 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.07(3H,s), 3.33(1H,dd,J=13.5, 10.0Hz), 3.55(1H,dd,J=13.5, 5.5Hz), 5.62(1H,m), 7.03(1H,s), 7.07-7.18(3H,m), 7.22-7.33(5H,m), 7.41(1H,d,J=7.5Hz), 7.60(1H,t,J=7.5Hz), 7.69(2H,t,J=7.5Hz), 7.77(1H,t,J=7.5Hz), 7.82(1H,d,J=7.5Hz), 8.02(1H,d,J=1.0Hz), 8.13(1H,d,J=7.5Hz), 8.80(1H,d,J=1.0Hz), 9.37(1H,br s)

Example 27

The object compound was obtained according to a similar manner to that of Example 1.

pale yellow amorphous solid

MASS (ESI) (m/z) : 451 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.08(3H,s), 3.38(1H,dd,J=13.5, 9.0Hz),
3.50(1H,dd,J=13.5, 6.0Hz), 3.82(3H,s), 5.64(1H,m),
6.92(2H,d,J=7.5Hz), 7.03-8.14(14H,m), 9.63(1H,br s)

Example 28

The object compound was obtained according to a similar manner to that of Example 1.

colorless solid

mp : 221-230.5℃

MASS (ESI) (m/z) : 451 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 3.32(2H,m), 3.70(3H,s), 4.74(2H,s),
5.62(1H,m), 6.67(1H,s), 6.71(2H,d,J=7.5Hz),
6.82(2H,d,J=7.5Hz), 6.93(1H,d,J=1.0Hz), 6.99-7.30(8H,m),
7.37(1H,d,J=7.5Hz), 7.56-7.65(2H,m), 9.50(1H,s)

Example 29

The object compound was obtained according to a similar manner to that of Example 1.

off-white solid

mp : 192.5-198℃

MASS (ESI) (m/z) : 405 $(M+H)^+$

^{1}H-NMR ($CDCl_3$, δ) 2.10(3H,s), 2.30-2.75(4H,m), 3.66(3H,s),
5.71(1H,q,J=7.5Hz), 6.95-7.04(2H,m), 7.11(1H,t,J=7.5Hz),
7.21-7.47(7H,m), 7.58(1H,d,J=7.5Hz), 7.63(1H,d,J=7.5Hz),
9.54(1H,s)

Example 30

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 532, 534 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.27-3.50(2H,m), 3.74(3H,s),
5.69-5.83(1H,m), 6.79(2H,d,J=8Hz), 6.88(1H,s),
7.04(2H,d,J=8Hz), 7.08-7.69(9H,m), 7.88(1H,s), 9.46(1H,br s)

Example 31

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 533, 535 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.30-3.49(2H,m), 3.75(3H,s), 5.68-5.82(1H,m), 6.79(2H,d,J=8Hz), 7.09(2H,d,J=8Hz), 7.20-7.80(10H,m), 7.89(1H,s)

Example 32

The object compound was obtained according to a similar manner to that of Example 1.

mp : 178-182℃

MASS : 465 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.42(3H,t,J=8Hz), 3.02(3H,s), 3.36-3.59(2H,m), 4.02(2H,q,J=8Hz), 5.67(1H,q,J=8Hz), 6.89(2H,d,J=8Hz), 7.01(1H,s), 7.03-7.13(6H,m), 7.17-7.30(4H,m), 7.38(1H,d,J=8Hz), 7.60(1H,d,J=8Hz), 8.48(1H,d,J=8Hz)

Example 33

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS : 466 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.42(3H,t,J=8Hz), 2.95(3H,s), 3.23-3.37(1H,m), 3.43-3.53(1H,m), 4.02(2H,q,J=8Hz), 5.45-5.58(1H,m), 6.90(2H,d,J=8Hz), 7.01(1H,s), 7.03-7.18(4H,m), 7.19-7.31(4H,m), 7.40(1H,t,J=8Hz), 7.43(1H,s), 7.51(1H,d,J=8Hz), 7.63(1H,d,J=8Hz), 7.81(1H,d,J=8Hz)

Example 34

The object compound was obtained according to a similar manner to that of Example 1.

mp : 174-178℃

MASS : 449 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.28(3H,t,J=8Hz), 2.69(2H,q,J=8Hz),
3.08(3H,s), 3.40-3.60(2H,m), 5.68-5.80(1H,m), 7.02-7.19(7H,m),
7.19-7.30(6H,m), 7.40(1H,d,J=8Hz), 7.61(1H,d,J=8Hz),
8.69(1H,d,J=8Hz)

Example 35

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS : 450 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.24(3H,t,J=8Hz), 2.69(2H,t,J=8Hz),
3.00(3H,s), 3.25-3.38(1H,m), 3.43-3.57(1H,m), 5.48-5.60(1H,m),
7.00-7.19(5H,m), 7.19-7.32(6H,m), 7.40(1H,t,J=8Hz),
7.45(1H,s), 7.51(1H,d,J=8Hz), 7.63(1H,d,J=8Hz),
7.81(1H,d,J=8Hz)

Example 36

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS : 485 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 2.93(3H,s), 3.30-3.50(2H,m), 3.70(3H,s),
5.53-5.63(1H,m), 6.71(2H,d,J=8Hz), 6.98(2H,d,J=8Hz),
7.00-7.12(3H,m), 7.16-7.40(5H,m), 7.42(1H,d,J=8Hz),
7.60(1H,d,J=8Hz), 8.40(1H,d,J=8Hz)

Example 37

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS : 465 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 2.39(3H,s), 3.10(3H,s), 3.30-3.50(2H,m),
3.70(3H,s), 5.61(1H,q,J=8Hz), 6.70(2H,d,J=8Hz),
6.99(2H,d,J=8Hz), 7.01-7.28(8H,m), 7.38(1H,d,J=8Hz),
7.60(1H,d,J=8Hz), 8.42(1H,d,J=8Hz)

Example 38

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS : 485 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 3.09(3H,s), 3.30-3.50(2H,m), 3.70(3H,s), 5.62(1H,q,J=8Hz), 6.70(2H,d,J=8Hz), 6.99(2H,d,J=8Hz), 7.01-7.29(6H,m), 7.29-7.40(3H,m), 7.59(1H,d,J=8Hz), 8.51(1H,d,J=8Hz)

Example 39

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS : 485 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 3.10(3H,s), 3.31-3.52(2H,m), 3.70(3H,s), 5.60-5.72(1H,m), 6.73(2H,d,J=8Hz), 7.01(2H,d,J=8Hz), 7.07-7.20(4H,m), 7.20-7.30(2H,m), 7.30-7.50(3H,m), 7.61(1H,d,J=8Hz), 8.59(1H,d,J=8Hz)

Example 40

The object compound was obtained according to a similar manner to that of Example 1.

amorphous solid

MASS : 469 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 3.08(3H,s), 3.30-3.40(2H,m), 3.71(3H,s), 5.67(1H,q,J=8Hz), 6.71(2H,d,J=8Hz), 7.00(2H,d,J=8Hz), 7.03-7.30(8H,m), 7.39(1H,d,J=8Hz), 7.60(1H,d,J=8Hz), 8.60(1H,d,J=8Hz)

Example 41

The object compound was obtained according to a similar manner to that of Example 1.

mp : 115-118℃

MASS : 495 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 1.42(3H,t,J=8Hz), 3.03(3H,s),
3.20-3.31(1H,m), 3.36-3.47(1H,m), 3.70(3H,s),
4.03(2H,q,J=8Hz), 5.48-5.59(1H,m), 6.73(2H,d,J=8Hz),
6.90(2H,d,J=8Hz), 6.99(2H,d,J=8Hz), 7.00(2H,s),
7.08-7.18(3H,m), 7.23(1H,t,J=8Hz), 7.39(1H,d,J=8Hz),
7.61(1H,d,J=8Hz), 7.86(1H,d,J=8Hz), 9.60(1H,s)

Example 42

The object compound was obtained according to a similar manner to that of Example 1.

mp : >250℃

MASS : 529 (M+1)

^{1}H-NMR ($CDCl_3$) δ : 3.17-3.40(2H,m), 3.52(3H,s), 3.68(3H,s),
5.49(1H,q,J=8Hz), 6.79(2H,d,J=8Hz), 7.01-7.18(2H,m),
7.07(1H,s), 7.21(2H,d,J=8Hz), 7.36(2H,d,J=8Hz),
7.39(1H,t,J=8Hz), 7.61(2H,d,J=8Hz), 8.09(1H,d,J=8Hz),
8.19(1H,d,J=8Hz), 8.39(1H,d,J=8Hz)

Example 43

The object compound was obtained according to a similar manner to that of Example 1.

pale yellow amorphous solid

MASS : 571 $(M+H)^+$

^{1}H-NMR ($CDCl_3$) δ : 1.16(3H,t,J=7.0Hz), 2.79(3H,s),
3.42(1H,dd,J=12.0 and 10.0Hz), 3.53(1H,dd,J=12.0 and 5.5Hz),
4.22(2H,q,J=7.0Hz), 5.53(1H,m), 6.98(1H,d,J=1.0Hz),
7.04-7.10(4H,m), 7.11(1H,t,J=7.5Hz), 7.20-7.30(4H,m),
7.33(1H,d,J=7.5Hz), 7.56(2H,d,J=7.5Hz), 7.64(1H,d,J=7.5Hz),
7.91(1H,br d,J=7.5Hz), 9.21(1H,br s)

Example 44

The object compound was obtained according to a similar manner to that of Example 1.

off-white solid

mp : 258.5-260℃

MASS : 421 $(M+H)^+$

^{1}H-NMR ($CDCl_3$) δ : 3.02(3H,s), 3.29(1H,dd,J=13.0 and 8.5Hz), 3.49(1H,dd,J=13.0 and 5.5Hz), 5.58(1H,m), 7.02-7.09(3H,m), 7.10(1H,s), 7.15(1H,d,J=7.5Hz), 7.20-7.43(10H,m), 7.66(1H,d,J=7.5Hz), 7.73(1H,d,J=7.5Hz), 9.48(1H,s)

Example 45

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 543, 545 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.39(3H,t,J=7Hz), 3.06(3H,s), 3.25(1H,dd,J=13 and 9Hz), 3.41(1H,dd,J=13 and 5Hz), 3.97(2H,q,J=7Hz), 5.46-5.61(1H,m), 6.75(2H,d,J=8Hz), 6.95(2H,d,J=8Hz), 7.00-7.70(10H,m), 7.90(1H,br d,J=8Hz), 9.55(1H,br s)

Example 46

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 544, 546 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.40(3H,t,J=7Hz), 3.04(3H,s), 3.22(1H,dd,J=13 and 9Hz), 3.41(1H,dd,J=13 and 5Hz), 3.98(2H,q,J=7Hz), 5.41-5.55(1H,m), 6.77(2H,d,J=8Hz), 6.98(2H,d,J=8Hz), 7.05-7.75(11H,m)

Example 47

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 529, 531 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.15(3H,s), 3.29-3.48(2H,m), 3.81(3H,s), 5.52-5.66(1H,m), 6.91(2H,d,J=8Hz), 6.97(2H,d,J=8Hz), 7.00(1H,s), 7.02-7.68(9H,m), 8.01(1H,br d,J=8Hz), 9.84(1H,br s)

Example 48

The object compound was obtained according to a similar manner to

that of Example 1.

MASS (ESI) (m/z) : 530, 532 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.12(3H,s), 3.25-3.48(2H,m), 3.82(3H,s), 5.45-5.60(1H,m), 6.93(2H,d,J=8Hz), 6.99(2H,d,J=8Hz), 7.03(1H,s), 7.11-7.70(10H,m)

Example 49

The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 495 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 1.39(3H,t,J=7Hz), 3.02(3H,s), 3.18-3.48(2H,m), 3.82(3H,s), 3.96(2H,q,J=7Hz), 5.45-5.59(1H,m), 6.74(2H,d,J=8Hz), 6.91(2H,d,J=8Hz), 6.95(2H,d,J=8Hz), 7.01(1H,s), 7.02-7.68(7H,m), 7.88(1H,br d,J=8Hz), 9.59(1H,br s)

Example 50

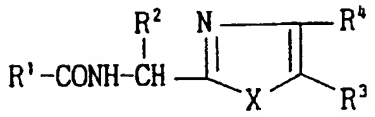
The object compound was obtained according to a similar manner to that of Example 1.

MASS (ESI) (m/z) : 481 $(M+H)^+$

^{1}H-NMR ($CDCl_3$,300MHz) δ : 3.04(3H,s), 3.19-3.48(2H,m), 3.74(3H,s), 3.82(3H,s), 5.47-5.61(1H,m), 6.74(2H,d,J=8Hz), 6.91(2H,d,J=8Hz), 6.98(2H,d,J=8Hz), 7.01(1H,s), 7.02-7.68(7H,m), 7.92(1H,br d,J=8Hz), 9.66(1H,br s)

CLAIMS

1. A compound of the formula :

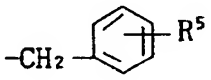


(I)

wherein

R^1 is indolyl or benzofuranyl;

R^2 is hydrogen, lower alkylthio(lower)alkyl or a group of the formula:



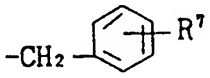
in which R^5 is hydrogen, lower alkoxy or halogen;

R^3 is hydrogen, quinolyl or phenyl which may have a suitable substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkylthio and halogen;

R^4 is hydrogen or optionally esterified carboxy; and

X is S or NR^6

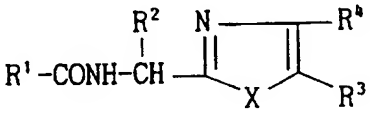
in which R^6 is hydrogen, lower alkyl or a group of the formula:



in which R^7 is lower alkyl or lower alkoxy,

and a pharmaceutically acceptable salt thereof.

2. A process for preparing a compound of the formula:

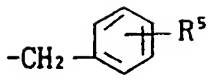


(I)

wherein

R^1 is indolyl or benzofuranyl;

R^2 is hydrogen, lower alkylthio(lower)alkyl or a group of the formula:



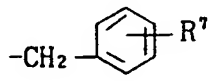
in which R^5 is hydrogen, lower alkoxy or halogen;

R^3 is hydrogen, quinolyl or phenyl which may have a suitable substituent selected from the group consisting of lower alkyl, lower alkoxy, lower alkylthio and halogen;

R^4 is hydrogen or optionally esterified carboxy; and

X is S or NR^6

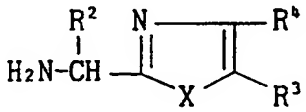
in which R^6 is hydrogen, lower alkyl or a group of the formula:



in which R^7 is lower alkyl or lower alkoxy,

or a salt thereof,

which comprises reacting a compound of the formula:



wherein R^2, R^3, R^4 and X are each as defined above, or its reactive derivative, or a salt thereof, with a compound of the formula:

$$R^1\text{-}COOH$$

wherein R^1 is as defined above, or its reactive derivative, or a salt thereof.

3. A pharmaceutical composition comprising the compound of Claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.

4. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof as a medicament.

5. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof as a medicament for prophylactic and therapeutic treatment of NO-mediated diseases.

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/JP 97/01757

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/12 A61K31/415 A61K31/425 C07D401/14 C07D405/12
C07D417/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 01817 A (ASTRA AB ;MACDONALD JAMES EDWIN (US); SHAKESPEARE WILLIAM CALVIN () 25 January 1996 see page 43; claim 1 see page 46; claims 15-17	1-5
P,Y	WO 96 16981 A (FUJISAWA PHARMACEUTICAL CO ;ITOH YOSHIKUNI (JP); IWAMOTO TOSHIRO () 6 June 1996 see page 689 - page 692; claim 1	1-5
Y	TETRAHEDRON LETTERS, vol. 34, no. 12, 19 March 1993, OXFORD GB, pages 1901-1904, XP002038851 T.D. GORDON ET AL.: "Synthetic Approaches to the 'Azole' Peptide Mimetics" see page 1901, paragraph 1	1-5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 1997	09.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Fink, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 97/01757

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 4 and 5 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna d Application No
PCT/JP 97/01757

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9601817 A	25-01-96	AU 2413995 A	09-02-96
		EP 0759027 A	26-02-97
		FI 964463 A	06-11-96
		NO 964698 A	06-11-96
WO 9616981 A	06-06-96	AU 3993795 A	19-06-96
		ZA 9510201 A	25-06-96

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